Clinical Dermatology
For Ruth, Patricia and Arlene
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Preface to the third edition

Five years is a long time in modern medicine, and we feel that the moment has come for Clinical Dermatology to move into its third edition. As before, every chapter has been updated extensively, but our aim is still the same—to create an easily read text that will help family doctors to get to grips with a subject many still find confusing, despite the increasingly stodgy sets of guidelines that now land regularly on their desks.

We have selected the best elements of these guidelines for our new sections on treatment, which are therefore much more ‘evidence based’. However, if we had to include only treatments based on flawless evidence, we would have to leave out too many old favourites that have stood the test of time, but have still not been evaluated properly. Next time perhaps.

We have also reacted to a survey of our readers, which showed that most of them spend little time on the chapters devoted only to the structure, function and immunology of the skin. We have pruned these back, but have put more physiology and pathology into the relevant clinical chapters where it should be of more use to a doctor struggling through a busy surgery.

Other changes too have been prompted by the helpful comments of our readers. They include a new chapter on regional dermatology, dealing with the special problems of areas such as the mouth and the genitalia; the replacement of several unloved clinical photographs; the insertion of a list of suggestions for further reading at the end of each chapter; more discussion of the ageing skin and of quality of life issues; and more emphasis on the types of surgery that can easily be undertaken by family doctors. More power to their elbows.

Finally, many important recent advances have entered every chapter on their own merits. Dermatoscopy, the expanding role of lasers, ‘sun sense’, and the drug treatment of AIDS are good examples of these. In addition, some new subjects, such as cutaneous anthrax, have been forced into the new edition by outside events.

We welcome you to our third edition.

Acknowledgements

Many of the clinical photographs come from the collection of the Department of Dermatology at the Royal Infirmary of Edinburgh and we wish to thank all those who presented them. We are most grateful to Graeme Chambers who has redrawn the previous line drawings as well as creating the new figures for the third edition, and to Geraldine Jeffers, Julie Elliott and Stuart Taylor of Blackwell Publishing for their help and encouragement in preparing this book.

We are also most grateful to the publishers for permission to use illustrations previously published in the following books:


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Some 10% of those who go to their family doctors do so with skin problems. We have seen an improvement in the way these have been managed over the last few years, but the subject still baffles many medical students—on both sides of the Atlantic. They find it hard to get a grip on the soggy mass of facts served up by some textbooks. For them we have tried to create an easily-read text with enough detail to clarify the subject but not enough to obscure it.

There are many doctors too who are puzzled by dermatology, even after years in practice. They have still to learn how to look at the skin with a trained eye. Anyone who denies that clinical dermatology is a visual specialty can never have practised it. In this book we have marked out the route to diagnostic success with a simple scheme for recognizing primary skin lesions using many diagrams and coloured plates.

We hope that this book will help both groups—students and doctors, including some in general medicine and some starting to train as dermatologists—and of course their patients. We make no apologies for our emphasis on diagnosis and management, and accept that we cannot include every remedy. Here, we mention only those preparations we have found to be useful and, to avoid too many trade names, we have tabulated those used in the UK and the USA in a Formulary at the back of the book.

We have decided not to break up the text by quoting lists of references. For those who want to know more there are many large and excellent textbooks on the shelves of all medical libraries.

While every effort has been made to ensure that the doses mentioned here are correct, the authors and publishers cannot accept responsibility for any errors in dosage which may have inadvertently entered this book. The reader is advised to check dosages, adverse effects, drug interactions, and contraindications in the latest edition of the British National Formulary or Drug Information (American Society of Hospital Pharmacists).
Introduction

Our overall aim in this book has been to make dermatology easy to understand by the many busy doctors who glimpsed it only briefly, if at all, during their medical training. All too often the subject has been squeezed out of its proper place in the undergraduate curriculum, leaving growing numbers who quail before the skin and its reputed 2000 conditions, each with its own diverse presentations. They can see the eruptions clearly enough, but cannot describe or identify them. There are no machines to help them. Even official ‘clinical guidelines’ for treatment are no use if a diagnosis has not been made. Their patients quickly sense weakness and lose faith. We hope that this book will give them confidence in their ability to make the right diagnosis and then to prescribe safe and effective treatment.

To do so they will need some understanding of the anatomy, physiology and immunology of the skin (Chapter 2): but, as Robert Willan (1757–1812) (Figure) (recently elected as ‘Dermatologist of the Millennium’) showed long ago, the simple steps that lead to a sensible working diagnosis must start with the identification of primary skin lesions and the patterns these have taken up on the skin surface (Chapter 3). After this has been achieved, investigations can be directed along sensible lines (Chapter 3) until a firm diagnosis is reached. Then, and only then, will the correct line of treatment snap into place.

But another cloud of mystery has settled here, over the subject of topical treatment. We attempt to blow this away with a few simple rules governing the selection of the right active ingredient, and of the right vehicle in which it should be put up (Chapter 23). Correct choices here will be repaid by good results. Patients may be quick to complain if they are not doing well; equally they are delighted if their eruptions can be seen to melt rapidly away. Many of them are now joining in the quest for cosmetic perfection that is already well advanced in the USA and becoming more fashionable in the UK. Family doctors who are asked about this topic can find their answers in our new chapter on physical methods of treatment (Chapter 24).

We do not pretend that all of the problems in the classification of skin diseases have been solved in this book. Far from it: some will remain as long as their causes are still unknown, but we make no apology for trying to keep our terminology as simple as possible. Many doctors are put off by the cumbersome Latin names left behind by earlier pseudo-botanical classifications. Names like painful nodule of the ear or ear corn must now be allowed to take over from more traditional ones such as chondrodermatitis nodularis helicis chronica, and fist fights over the difference between dermatitis and eczema must now stop.

As well as simplifying the terminology, we have concentrated mainly on common conditions, which make up the bulk of dermatology in developed countries, though we do mention some others, which may be rare, but which illustrate important general principles. We have also tried to cut out as many synonyms and eponyms as possible. We have included some further reading at the end of each chapter for those wanting more information and, for the connoisseur,
the names of some reference books at the end of this section.

We have, wherever possible, grouped together conditions that have the same cause, e.g. fungal infections (Chapter 14) and drug reactions (Chapter 22). Failing this, some chapters are based on a shared physiology, e.g. disorders of keratinization (Chapter 4) or on a shared anatomy, e.g. disorders of hair and nails (Chapter 13), of blood vessels (Chapter 11) or of the sweat glands (Chapter 12). In some chapters we have, reluctantly, been forced to group together conditions that share physical characteristics, e.g. the bullous diseases (Chapter 9) and the papulosquamous disorders (Chapter 6): but this is unsound, and brings together some strange bedfellows. Modern research will surely soon reallocate their positions in the dormitory of dermatology. Finally, we must mention, sooner rather than later, electronic communication and the help that it can offer both patients and doctors. Web sites are proliferating almost as rapidly as the epidermal cells in psoriasis; this section deserves its own heading.

Dermatology on the Internet

The best web sites are packed with useful information: others are less trustworthy. We rely heavily on those of the British Association of Dermatologists (www.bad.org.uk) and the American Academy of Dermatology (www.aad.org) for current guidelines on how to manage a variety of individual skin conditions. They also provide excellent patient information leaflets, and the addresses of patient support groups. The British Dermatologists Internet Site (www.bdis.org.uk) offers further guidelines for British general practitioners on the management of common skin diseases, including advice on when to refer them to a dermatologist.

Two other favourite sites are linked lists of dermatology websites (www.fammed.wisc.edu/education/presentation/derm/Dermcurriculum.html and www.medwebplus.com/subject/Dermatology). They provide many images of skin diseases, dermatology quizzes and lectures, interactive cases, and even an electronic textbook of dermatology. Finally, it is becoming easier to browse through dermatology journals online (www.mednets.com/dermatoljournals.htm). The full text of over half of the world’s 200 most cited journals is now available on a web site (http://highwire.stanford.edu) that includes the famous ‘Topic map’: few pleasures exceed that of ‘exploding’ clinical medicine into its subcategories by a process of simple clicking and dragging.

Further reading


Dermatology is the study of the skin and its associated structures, including the hair and nails, and of their diseases. It is an immense subject, embracing some 2000 conditions, yet, paradoxically, some 70% of the dermatology work in the UK is caused by only nine types of skin disorder (Table 1.1). Similarly, in the USA, nearly half of all visits to dermatologists are for one of three diagnoses: acne, warts and skin tumours. Things are very different in developing countries where overcrowding and poor sanitation play a major part. There, skin disorders are even more common, particularly in the young, but are dominated by infections and infestations—the so-called ‘dermatoses of poverty’—amplified by the presence of HIV infection.

A sense of perspective is important, and this chapter presents an overview of the causes, prevalence and impact of skin disease.

### Causes

The skin is the boundary between ourselves and the world around us. It is an important sense organ, and controls heat and water loss. It reflects internal changes (Chapter 19) and reacts to external ones. Usually, it adapts easily and returns to a normal state, but sometimes it fails to do so and a skin disorder appears. Some of the internal and external factors that are important causes of skin disease are shown in Fig. 1.1. Often several will be operating at the same time; just as often, no obvious cause for a skin abnormality can be found—and here lies much of the difficulty of dermatology. Nevertheless, when a cause is obvious, such as the washing of dishes and the appearance of irritant hand dermatitis, or sunburn and the development of melanoma, education and prevention are just as important as treatment.

### Prevalence

No one who has worked in any branch of medicine will doubt the importance of diseases of the skin. A neurologist, for example, will know all about the Sturge–Weber syndrome, a gastroenterologist about the Peutz–Jeghers syndrome, and a cardiologist about the LEOPARD syndrome; but even in their own wards they will see far more of other common skin conditions such as drug eruptions, seborrheic eczema and scabies. They should know about these too.

In primary care, skin problems are even more important, and the prevalence of some common skin conditions, such as skin cancer and atopic eczema, is undoubtedly rising. Currently, skin disorders account for about 15% of all consultations in general practice in the UK, but this is only the tip of an iceberg of skin disease, the sunken part of which consists of problems that never get to doctors, being dealt with or ignored in the community.

How large is this problem? No one quite knows, as those who are not keen to see their doctors seldom star in the medical literature. The results of a study of

<table>
<thead>
<tr>
<th>Table 1.1 The most common categories of skin disorder in the UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Viral warts</td>
</tr>
<tr>
<td>Other infective skin disorders</td>
</tr>
<tr>
<td>Benign tumours and vascular lesions</td>
</tr>
<tr>
<td>Leg ulcers</td>
</tr>
<tr>
<td>Contact dermatitis and other eczemas</td>
</tr>
</tbody>
</table>
A community study of adults in the UK found 22.5% to have a skin disease needing medical attention: only one in five of these had seen a doctor within the preceding 6 months. Self-medication was far more common than any treatment prescribed by doctors.

In another UK study, 14% of adults and 19% of children had used a skin medication during the previous 2 weeks; only one-tenth of these were prescribed by doctors.

Several large studies have confirmed that this is the case with other skin diseases too.

- Of a large representative sample of the US population, 31.2% were found to have significant skin disease that deserved medical attention. Scaled up, these figures suggest that some 80 million of the US population may have significant skin diseases.

The responses to minor ailments of all types are shown in Table 1.2; clearly a few sufferers took more than one course of action. These responses apply to skin disorders too, and form the basis for the ‘iceberg’ of psoriasis in the UK shown in Fig. 1.2. In the course of a single year most of those with psoriasis see no doctor, and only a few will see a dermatologist. Some may have fallen victim to fraudulent practices, such as ‘herbal’ preparations laced with steroids, and baseless advice on ‘allergies’.

Table 1.2 Responses to minor ailments.

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not use anything</td>
<td>45%</td>
</tr>
<tr>
<td>Used a home remedy</td>
<td>9%</td>
</tr>
<tr>
<td>Used an over-the-counter remedy</td>
<td>24%</td>
</tr>
<tr>
<td>Used a prescription remedy already in the house</td>
<td>13%</td>
</tr>
<tr>
<td>Saw a doctor</td>
<td>13%</td>
</tr>
</tbody>
</table>

Fig. 1.1 Some internal and external factors causing skin diseases.

Fig. 1.2 The ‘iceberg’ of psoriasis in the UK during a single year.

- A community study of adults in the UK found 22.5% to have a skin disease needing medical attention: only one in five of these had seen a doctor within the preceding 6 months. Self-medication was far more common than any treatment prescribed by doctors.
- In another UK study, 14% of adults and 19% of children had used a skin medication during the previous 2 weeks; only one-tenth of these were prescribed by doctors.
prevalence of skin tumours steadily mounts with age (Fig. 1.4).

The pattern of skin disease in a community depends on many other factors too, both genetic and environmental; some are listed in Table 1.3.

### Table 1.3 Some factors influencing the prevalence of skin diseases in a community.

<table>
<thead>
<tr>
<th>High level of</th>
<th>High incidence of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet radiation</td>
<td>Skin malignancy in Caucasians</td>
</tr>
<tr>
<td>Heat and humidity</td>
<td>Fungal and bacterial infections</td>
</tr>
<tr>
<td>Industrialization</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>Underdevelopment</td>
<td>Infestations</td>
</tr>
<tr>
<td></td>
<td>Bacterial and fungal infections</td>
</tr>
</tbody>
</table>

Every 10 years or so we are given a snapshot of the way skin disorders are being dealt with in the UK, in a series of reports entitled *Morbidity Statistics from General Practice*. Some of the details from these, and from other studies, are given in Fig. 1.3. In addition, within each community, different age groups suffer from different skin conditions. In the USA, for example, diseases of the sebaceous glands (mainly acne) peak at the age of about 18 years and then decline, while the prevalence of skin tumours steadily mounts with age (Fig. 1.4).

The pattern of skin disease in a community depends on many other factors too, both genetic and environmental; some are listed in Table 1.3.

### Impact

Much of this book is taken up with ways in which skin diseases can do harm. Most fit into the five Ds shown in Fig. 1.5; others are more subtle. Topical treatment, for example, can seem illogical to those who think that their skin disease is emotional in origin; it has been shown recently that psoriasis with great disability comply especially poorly with topical treatment.
In addition, the problems created by skin disease do not necessarily tally with the extent and severity of the eruption as judged by an outside observer. Quality-of-life studies give a different, patient-based, view of skin conditions. Questionnaires have been designed to compare the impact of skin diseases with those of other conditions; patients with bad psoriasis, for example, have at least as great a disability as those with angina. In the background lurk problems due to the costs of treatment and time lost from work.

Disfigurement
The possible reactions to disfiguring skin disease are described on p. 294. They range from a leper complex (e.g. some patients with psoriasis, p. 294), to embarrassment (e.g. port-wine stains, Fig. 1.6) or androgenetic alopecia in both men and women (p. 166). Disorders of body image can lead those who have no skin disease to think that they have, and even to commit suicide in this mistaken belief (dermatological non-disease, p. 295).

Discomfort
Some people prefer pain to itch; skin diseases can provide both. Itchy skin disorders include eczema (p. 70), lichen planus (p. 64), scabies (p. 227) and dermatitis herpetiformis (p. 113). Pain is marked in shingles (p. 206), leg ulcers (p. 139) and glomus tumours (p. 277).

Disability
Skin conditions are capable of ruining the quality of anyone’s life. Each carries its own set of problems. At the most obvious level, dermatitis of the hands can quickly destroy a manual worker’s earning capacity, as many hairdressers, nurses, cooks and mechanics know to their cost. In the USA, skin diseases account for almost half of all cases of occupational illness and cause more than 50 million days to be lost from work each year.

Disability and disfigurement can blend in a more subtle way, so that, for example, in times of unem-
Employment people with acne find it hard to get jobs. Psoriatics in the USA, already plagued by tactless hairdressers and messy treatments, have been shown to lose thousands of dollars in earnings by virtue of time taken off work. Even trivial psoriasis on the fingertips of blind people can have a huge effect on their lives by making it impossible to read Braille.

Depression

The physical, sensory and functional problems listed above often lead to depression and anxiety, even in the most stable people. Depression also seems to modulate the perception of itching, which becomes much worse. Feelings of stigmatization and rejection are common in patients with chronic skin diseases: up to 10% of patients with psoriasis that they think is bad have had suicidal thoughts. The risk of suicide in patients with severe acne is discussed on p. 155.

Death

Deaths from skin disease are fortunately rare, but they do occur (e.g. in pemphigus, toxic epidermal necrolysis and cutaneous malignancies). In addition, the stresses generated by a chronic skin disorder such as psoriasis predispose to heavy smoking and drinking, which carry their own risks.

In this context, the concept of skin failure is an important one. It may occur when any inflammatory skin disease becomes so widespread that it prevents normal functioning of the skin, with the results listed in Table 1.4. Its causes include erythroderma (p. 69), toxic epidermal necrolysis (p. 115), severe erythema multiforme (p. 99), pustular psoriasis (p. 53) and pemphigus (p. 108).

**Further reading**


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**Table 1.4** The consequences of skin failure.

<table>
<thead>
<tr>
<th>Function</th>
<th>Skin failure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature control</td>
<td>Cannot sweat when too hot; cannot vasoconstrict when too cold. Hence temperature swings dangerously up and down</td>
<td>Controlled environmental temperature</td>
</tr>
<tr>
<td>Barrier function</td>
<td>Raw skin surfaces lose much fluid and electrolytes</td>
<td>Monitor and replace High protein diet Antibiotic. Bathing/wet compresses</td>
</tr>
<tr>
<td></td>
<td>Heavy protein loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial pathogens multiply on damaged skin</td>
<td></td>
</tr>
<tr>
<td>Cutaneous blood flow</td>
<td>Shunt through skin may lead to high output cardiac failure in those with poor cardiac reserve</td>
<td>Aggressively treat skin Support vital signs</td>
</tr>
<tr>
<td>Others</td>
<td>Erythroderma may lead to malabsorption</td>
<td>Usually none needed Regrow spontaneously Nurse as for burns</td>
</tr>
<tr>
<td></td>
<td>Hair and nail loss later</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nursing problems handling patients particularly with toxic epidermal necrolysis (p. 115) and pemphigus (p. 108)</td>
<td></td>
</tr>
</tbody>
</table>


The skin—the interface between humans and their environment—is the largest organ in the body. It weighs an average of 4 kg and covers an area of 2 m². It acts as a barrier, protecting the body from harsh external conditions and preventing the loss of important body constituents, especially water. A death from destruction of skin, as in a burn, or in toxic epidermal necrolysis (p. 115), and the misery of unpleasant acne, remind us of its many important functions, which range from the vital to the cosmetic (Table 2.1).

The skin has two layers. The outer is epithelial, the *epidermis*, which is firmly attached to, and supported by connective tissue in the underlying *dermis*. Beneath the dermis is loose connective tissue, the *subcutis/hypodermin* which usually contains abundant fat (Fig. 2.1).

**Epidermis**

The epidermis is formed from many layers of closely packed cells, the most superficial of which are flattened and filled with keratins; it is therefore a stratified squamous epithelium. It adheres to the dermis partly by the interlocking of its downward projections (*epidermal ridges or pegs*) with upward projections of the dermis (*dermal papillae*) (Fig. 2.1).

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### Table 2.1 Functions of the skin.

<table>
<thead>
<tr>
<th>Protection against:</th>
<th>Structure/cell involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemicals, particles</td>
<td>Horny layer</td>
</tr>
<tr>
<td>ultraviolet radiation</td>
<td>Melanocytes</td>
</tr>
<tr>
<td>antigens, haptens</td>
<td>Langerhans cells</td>
</tr>
<tr>
<td>microbes</td>
<td>Langerhans cells</td>
</tr>
<tr>
<td>Preservation of a balanced internal environment</td>
<td>Horny layer</td>
</tr>
<tr>
<td>Prevents loss of water, electrolytes and macromolecules</td>
<td>Horny layer</td>
</tr>
<tr>
<td>Shock absorber</td>
<td>Dermis and subcutaneous fat</td>
</tr>
<tr>
<td>Strong, yet elastic and compliant</td>
<td>Blood vessels</td>
</tr>
<tr>
<td>Temperature regulation</td>
<td>Eccrine sweat glands</td>
</tr>
<tr>
<td>Insulation</td>
<td>Subcutaneous fat</td>
</tr>
<tr>
<td>Sensation</td>
<td>Specialized nerve endings</td>
</tr>
<tr>
<td>Lubrication</td>
<td>Sebaceous glands</td>
</tr>
<tr>
<td>Protection and prising</td>
<td>Nails</td>
</tr>
<tr>
<td>Calorie reserve</td>
<td>Subcutaneous fat</td>
</tr>
<tr>
<td>Vitamin D synthesis</td>
<td>Keratinocytes</td>
</tr>
<tr>
<td>Body odour/pheromones</td>
<td>Apocrine sweat glands</td>
</tr>
<tr>
<td>Psychosocial, display</td>
<td>Skin, lips, hair and nails</td>
</tr>
</tbody>
</table>
sprout many fine processes and hemidesmosomes, anchoring them to the lamina densa of the basement membrane.

In normal skin some 30% of basal cells are preparing for division (growth fraction). Following mitosis, a cell enters the G₁ phase, synthesizes RNA and protein, and grows in size (Fig. 2.3). Later, when the cell is triggered to divide, DNA is synthesized (S phase) and chromosomal DNA is replicated. A short postsynthetic (G₂) phase of further growth occurs before mitosis (M). DNA synthesis continues through the S and G₂ phases, but not during mitosis. The G₁ phase is then repeated, and one of the daughter cells moves into the suprabasal layer. It then differentiates (Fig. 2.2), having lost the capacity to divide, and synthesizes keratins. Some basal cells remain inactive in a so-called G₀ phase but may re-enter the cycle and resume proliferation. The

The epidermis contains no blood vessels. It varies in thickness from less than 0.1 mm on the eyelids to nearly 1 mm on the palms and soles. As dead surface squames are shed (accounting for some of the dust in our houses), the thickness is kept constant by cells dividing in the deepest (basal or germinative) layer. A generated cell moves, or is pushed by underlying mitotic activity, to the surface, passing through the prickle and granular cell layers before dying in the horny layer. The journey from the basal layer to the surface (epidermal turnover or transit time) takes about 60 days. During this time the appearance of the cell changes. A vertical section through the epidermis summarizes the life history of a single epidermal cell (Fig. 2.2).

The basal layer, the deepest layer, rests on a basement membrane, which attaches it to the dermis. It is a single layer of columnar cells, whose basal surfaces

Fig. 2.1 Three-dimensional diagram of the skin, including a hair follicle.
of the arrector pili muscle but cannot be identified by histology. These cells divide infrequently, but can generate new proliferative cells in the epidermis and hair follicle in response to damage.

### Keratinocytes

The *spinous or prickle cell* layer (Fig. 2.4) is composed of *keratinocytes*. These differentiating cells, which synthesize keratins, are larger than basal cells. Keratinocytes are firmly attached to each other by small interlocking cytoplasmic processes, by abundant desmosomes and by an intercellular cement of glycoproteins and lipoproteins. Under the light microscope, the desmosomes look like ‘prickles’. They are specialized attachment plaques that have been characterized biochemically. They contain desmoplakins, desmogleins and desmocollins. Autoantibodies to these proteins are found in pemphigus (p. 108), when they are responsible for the detachment of keratinocytes from one another and so for intraepidermal blister formation. Cytoplasmic continuity between keratinocytes occurs at *gap junctions*, specialized areas on opposing cell walls. Tonofilaments are small fibres running from the
leading to keratinization and the formation of a thick and tough peripheral protein coating called the *horny envelope*. Its structural proteins include loricrin and involucrin, the latter binding to ceramides in the surrounding intercellular space under the influence of transglutaminase. Filaggrin, involucrin and loricrin can all be detected histochemically and are useful as markers of epidermal differentiation.

The *horny layer* (stratum corneum) is made of piled-up layers of flattened dead cells (corneocytes)—the bricks—stuck together by lipids—the mortar—in the intercellular space. The corneocyte cytoplasm is packed with keratin filaments, embedded in a matrix and enclosed by an envelope derived from the keratohyalin granules. This envelope, along with the aggregated keratins that it encloses, gives the corneocyte its toughness, allowing the skin to withstand all sorts of chemical and mechanical insults. Horny cells normally have no nuclei or intracytoplasmic organelles, these having been destroyed by hydrolytic and degrading enzymes found in lamellar granules and the lysosomes of granular cells.

**Keratinization**

All cells have an internal skeleton made up of microfilaments (7 nm diameter; actin), microtubules (20–35 nm
horny layer. Desquamation is normally responsible for the removal of harmful exogenous substances from the skin surface. The cells lost are replaced by newly formed corneocytes; regeneration and turnover of the horny layer is therefore continuous.

The epidermal barrier

The horny layer prevents the loss of interstitial fluid from within, and acts as a barrier to the penetration of potentially harmful substances from outside. Solvent extraction of the epidermis leads to an increased permeability to water, and it has been known for years that essential fatty acid deficiency causes poor cutaneous barrier function. These facts implicate ceramides, cholesterol, free fatty acids (from lamellar granules; p. 10), and smaller quantities of other lipids, in cutaneous barrier formation. Barrier function is also impaired when the horny layer is removed experimentally, by successive strippings with adhesive tape, or clinically, by injury or skin disease. It is also decreased by excessive hydration or dehydration of the horny layer and by detergents.

The rate of penetration of a substance through the epidermis is directly proportional to its concentration difference across the barrier layer, and indirectly proportional to the thickness of the horny layer. A rise in skin temperature aids penetration. A normal horny layer is slightly permeable to water, but relatively impermeable to ions such as sodium and potassium. Some other substances (e.g. glucose and urea) also penetrate poorly, whereas some aliphatic alcohols pass through easily. The penetration of a solute dissolved in an organic liquid depends mainly on the qualities of the solvent.

Epidermopoiesis and its regulation

Both the thickness of the normal epidermis, and the number of cells in it, remain constant, as cell loss at the surface is balanced by cell production in the basal layer. Locally produced polypeptides (cytokines), growth factors and hormones stimulate or inhibit epidermal proliferation, interacting in complex ways to ensure homeostasis. Cytokines and growth factors (Table 2.2) are produced by keratinocytes, Langerhans cells, fibroblasts and lymphocytes within the skin. After these bind to high affinity cell surface receptors, DNA synthesis is controlled by signal transduction,
Melanocytes

Melanocytes are the only cells that can synthesize melanin. They migrate from the neural crest into the basal layer of the ectoderm where, in human embryos, they are seen as early as the eighth week of gestation. They are also found in hair bulbs, the retina and pia arachnoid. Each dendritic melanocyte associates with a number of keratinocytes, forming an ‘epidermal melanin unit’ (Fig. 2.5). The dendritic processes of melanocytes wind between the epidermal cells and end as discs in contact with them. Their cytoplasm contains discrete organelles, the melanosomes, containing varying amounts of the pigment melanin (Fig. 2.6).

Vitamin D synthesis

The steroid 7-dehydrocholesterol, found in keratinocytes, is converted by sunlight to cholecalciferol. The vitamin becomes active after 25-hydroxylation in the kidney. Lack of sun and kidney disease can both cause vitamin D deficiency and rickets.

Other cells in the epidermis

Keratinocytes make up about 85% of cells in the epidermis, but three other types of cell are also found there: melanocytes, Langerhans cells and Merkel cells. (Fig. 2.5).

<table>
<thead>
<tr>
<th>Designation</th>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interleukins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1</td>
<td>Interleukin 1</td>
<td>Lymphocyte activation</td>
</tr>
<tr>
<td>IL-3</td>
<td>Interleukin 3</td>
<td>Langerhans cell activation</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
<td>Acute phase reactions</td>
</tr>
<tr>
<td>IL-8</td>
<td>Interleukin 8</td>
<td>Colony-stimulating factor</td>
</tr>
<tr>
<td>IL-10</td>
<td>Interleukin 10</td>
<td>B-cell differentiation</td>
</tr>
<tr>
<td>IL-12</td>
<td>Interleukin 12</td>
<td>Chemotaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of TH-1 T cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induction of TH-2 T cells</td>
</tr>
<tr>
<td><strong>Colony stimulating factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte–macrophage colony-stimulating factor</td>
<td>Proliferation of granulocytes and macrophages</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte colony-stimulating factor</td>
<td>Proliferation of granulocytes</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Macrophage colony-stimulating factor</td>
<td>Proliferation of macrophages</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF</td>
<td>Transforming growth factors</td>
<td>Inhibit inflammation</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factors</td>
<td>Induce Class I antigens</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Interferon-α</td>
<td>Antiviral states</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon-γ</td>
<td>Antiviral state</td>
</tr>
</tbody>
</table>

involving protein kinase C or inositol phosphate. Catecholamines, which do not penetrate the surface of cells, influence cell division via the adenosine 3′, 5′-cyclic monophosphate (cAMP) second messenger system. Steroid hormones bind to receptor proteins within the cytoplasm, and then pass to the nucleus where they influence transcription.

Langerhans cells

The Langerhans cell is a dendritic cell (Figs 2.5 and 2.7) like the melanocyte. It also lacks desmosomes and tonofibrils, but has a lobulated nucleus. The specific
Fig. 2.5 Melanocyte, Langerhans cell and Merkel cell.

Fig. 2.6 Melanocyte (electron micrograph), with melanosomes (inset).
Langerhans cells have a key role in many immune reactions. They take up exogenous antigen, process it and present it to T lymphocytes either in the skin or in the local lymph nodes (p. 27). They probably play a part in immunosurveillance for viral and tumour antigens. In this way, ultraviolet radiation can induce skin tumours both by causing mutations in the epidermal cells, and by decreasing the number of epidermal Langerhans cells, so that cells bearing altered antigens are not recognized or destroyed by the immune system. Topical or systemic glucocorticoids also reduce the density of epidermal Langerhans cells. The Langerhans cell is the principal cell in skin allografts to which the T lymphocytes of the host react during rejection; allograft survival can be prolonged by depleting Langerhans cells.

Merkel cells

Merkel cells are found in normal epidermis (Fig. 2.5) and act as transducers for fine touch. They are non-dendritic cells, lying in or near the basal layer, and are of the same size as keratinocytes. They are concentrated in localized thickenings of the epidermis near hair follicles (hair discs), and contain membrane-bound spherical granules, 80–100 nm in diameter, which have a core of varying density, separated from the membrane by a clear halo. Sparse desmosomes connect these cells to neighbouring keratinocytes. Fine unmyelinated nerve endings are often associated with Merkel cells, which express immunoreactivity for various neuropeptides.
FUNCTION AND STRUCTURE OF SKIN

Laminins, large non-collagen glycoproteins produced by keratinocytes, aided by entactin, promote adhesion between the basal cells above the lamina lucida and type IV collagen, the main constituent of the lamina densa, below it. The laminins act as a glue, helping to hold the epidermis onto the dermis. Bullous pemphigoid antigens (of molecular weights 230 and 180 kDa) are synthesized by basal cells and are found in close association with the hemidesmosomes and laminin. Their function is unknown but antibodies to them are found in pemphigoid (p. 111), a subcutaneous blistering condition.

The dermo-epidermal junction

The basement membrane lies at the interface between the epidermis and dermis. With light microscopy it can be highlighted using a periodic acid–Schiff (PAS) stain, because of its abundance of neutral mucopolysaccharides. Electron microscopy (Fig. 2.9) shows that the lamina densa (rich in type IV collagen) is separated from the basal cells by an electron-lucent area, the lamina lucida. The plasma membrane of basal cells has hemidesmosomes (containing bullous pemphigoid antigens, collagen XVII and α6 β4 integrin). The lamina lucida contains the adhesive macromolecules, laminin-1, laminin-5 and entactin. Fine anchoring filaments (of laminin-5) cross the lamina lucida and connect the lamina densa to the plasma membrane of the basal cells. Anchoring fibrils (of type VII collagen), dermal microfibril bundles and single small collagen fibres (types I and III), extend from the papillary dermis to the deep part of the lamina densa.

Epidermal appendages

The skin appendages are derived from epithelial germs during embryogenesis and, except for the nails, lie in the dermis. They include hair, nails and sweat and sebaceous glands. They are described, along with the diseases that affect them, in Chapters 12 and 13, respectively.

Fig. 2.9 Structure and molecular composition of the dermo-epidermal junction.
epidermis, the rete pegs. This interdigitation is responsible for the ridges seen most readily on the fingertips (as fingerprints). It is important in the adhesion between epidermis and dermis as it increases the area of contact between them.

Like all connective tissues the dermis has three components: cells, fibres and amorphous ground substance.

Cells of the dermis

The main cells of the dermis are fibroblasts, but there are also small numbers of resident and transitory mononuclear phagocytes, lymphocytes, Langerhans cells and mast cells. Other blood cells, e.g. polymorphs, are seen during inflammation. The main functions of the resident dermal cells are listed in Table 2.3 and their role in immunological reactions is discussed later in this chapter.

Fibres of the dermis

The dermis is largely made up of interwoven fibres, principally of collagen, packed in bundles. Those in the papillary dermis are finer than those in the deeper reticular dermis. When the skin is stretched, collagen, with its high tensile strength, prevents tearing, and the elastic fibres, intermingled with the collagen, later return it to the unstretched state.

Collagen makes up 70–80% of the dry weight of the dermis. Its fibres are composed of thinner fibrils, which are in turn made up of microfibrils built from individual collagen molecules. These molecules consist of three polypeptide chains (molecular weight 150 kDa) forming a triple helix with a non-helical segment at both ends. The alignment of the chains is stabilized by covalent cross-links involving lysine and hydroxylysine. Collagen is an unusual protein as it contains a high proportion of proline and hydroxyproline and many glycine residues; the spacing of glycine as every third amino acid is a prerequisite for the formation of a triple helix. Defects in the enzymes needed for collagen synthesis are responsible for some skin diseases, including the Ehlers–Danlos syndrome (Chapter 21), and conditions involving other systems, including lathyrism (fragility of skin and other connective tissues) and osteogenesis imperfecta (fragility of bones).

There are many, genetically distinct, collagen proteins, all with triple helical molecules, and all rich in hydroxyproline and hydroxylysine. The distribution of some of them is summarized in Table 2.4.

<table>
<thead>
<tr>
<th>Collagen type</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Most connective tissues including tendon and bone</td>
</tr>
<tr>
<td></td>
<td>Accounts for approximately 85% of skin collagen</td>
</tr>
<tr>
<td>II</td>
<td>Cartilage</td>
</tr>
<tr>
<td>III</td>
<td>Accounts for about 15% of skin collagen</td>
</tr>
<tr>
<td></td>
<td>Blood vessels</td>
</tr>
<tr>
<td>IV</td>
<td>Skin (lamina densa) and basement membranes of other tissues</td>
</tr>
<tr>
<td>V</td>
<td>Ubiquitous, including placenta</td>
</tr>
<tr>
<td>VII</td>
<td>Skin (anchoring fibrils)</td>
</tr>
<tr>
<td></td>
<td>Fetal membranes</td>
</tr>
</tbody>
</table>
Reticulin fibres are fine collagen fibres, seen in fetal skin and around the blood vessels and appendages of adult skin.

Elastic fibres account for about 2% of the dry weight of adult dermis. They have two distinct protein components: an amorphous elastin core and a surrounding ‘elastic tissue microfibrillar component’. Elastin (molecular weight 72 kDa) is made up of polypeptides (rich in glycine, desmosine and valine) linked to the microfibrillar component through their desmosine residues. Abnormalities in the elastic tissue cause cutis laxa (sagging inelastic skin) and pseudoxanthoma elasticum (Chapter 21).

**Ground substance of the dermis**

The amorphous ground substance of the dermis consists largely of two glycosaminoglycans (hyaluronic acid and dermatan sulphate) with smaller amounts of heparan sulphate and chondroitin sulphate. The glycosaminoglycans are complexed to core protein and exist as proteoglycans.

The ground substance has several important functions:
- it binds water, allowing nutrients, hormones and waste products to pass through the dermis;
- it acts as a lubricant between the collagen and elastic fibre networks during skin movement; and
- it provides bulk, allowing the dermis to act as a shock absorber.

**Muscles**

Both smooth and striated muscle are found in the skin. The smooth arrector pili muscles (see Fig. 13.1) are used by animals to raise their fur and so protect them from the cold. They are vestigial in humans, but may help to express sebum. Smooth muscle is also responsible for ‘goose pimples’ (bumps) from cold, nipple erection, and the raising of the scrotum by the dartos muscle. Striated fibres (e.g. the platysma) and some of the muscles of facial expression, are also found in the dermis.

**Blood vessels**

Although the skin consumes little oxygen, its abundant blood supply regulates body temperature. The blood vessels lie in two main horizontal layers (Fig. 2.10). The deep plexus is just above the subcutaneous fat, and its arterioles supply the sweat glands and hair papillae. The superficial plexus is in the papillary dermis and arterioles from it become capillary loops in the dermal papillae. An arteriole arising in the deep dermis supplies an inverted cone of tissue, with its base at the epidermis.

The blood vessels in the skin are important in thermoregulation. Under sympathetic nervous control, arteriovenous anastomoses at the level of the deep plexus can shunt blood to the venous plexus at the expense of the capillary loops, thereby reducing surface heat loss by convection.

**Cutaneous lymphatics**

Afferent lymphatics begin as blind-ended capillaries in the dermal papilla and pass to a superficial lymphatic plexus in the papillary dermis. There are also two deeper horizontal plexuses, and collecting lymphatics from the deeper one run with the veins in the superficial fascia.

**Nerves**

The skin is liberally supplied with an estimated one million nerve fibres. Most are found in the face and extremities. Their cell bodies lie in the dorsal root ganglia. Both myelinated and non-myelinated fibres exist, with the latter making up an increasing proportion peripherally. Most free sensory nerves end in the dermis; however, a few non-myelinated nerve endings penetrate into the epidermis. Some of these are associated with Merkel cells (p. 14). Free nerve endings detect the potentially damaging stimuli of heat.
and pain (nocioceptors), while specialized end organs in the dermis, Pacinian and Meissner corpuscles, register deformation of the skin caused by pressure (mechanoreceptors) as well as vibration and touch. Autonomic nerves supply the blood vessels, sweat glands and arrector pili muscles.

Itching is an important feature of many skin diseases. It follows the stimulation of fine free nerve endings lying close to the dermo-epidermal junction. Areas with a high density of such endings (itch spots) are especially sensitive to itch-provoking stimuli. Impulses from these free endings pass centrally in two ways: quickly along myelinated A fibres, and more slowly along non-myelinated C fibres. As a result, itch has two components: a quick localized pricking sensation followed by a slow burning diffuse itching.

Many stimuli can induce itching (electrical, chemical and mechanical). In itchy skin diseases, pruritogenic chemicals such as histamine and proteolytic enzymes are liberated close to the dermoepidermal junction. The detailed pharmacology of individual diseases is still poorly understood but prostaglandins potentiate chemically induced itching in inflammatory skin diseases.

The skin immune system

The horny layer of the skin is able both to prevent the loss of fluid and electrolytes, and to stop the penetration of harmful substances (p. 11). It is a dry mechanical barrier from which contaminating organisms and chemicals are continually being removed by washing and desquamation. Only when these breach the horny layer do the cellular components, described below, come into play. The skin is involved in so many immunological reactions, seen regularly in the clinic (e.g. urticaria, allergic contact dermatitis, psoriasis, vasculitis), that a special mention has to be made of the peripheral arm of the immune system based in the skin—the skin immune system (SIS).

The idea of an SIS as a functionally independent immunological unit is helpful. It includes the cutaneous blood vessels and lymphatics with their local lymph nodes and contains circulating lymphocytes and resident immune cells. Although it is beyond the scope of this book to cover general immunology, this section outlines some of the intricate ways in which antigens are recognized by specialized skin cells, mainly the Langerhans cells, and how antibodies, lymphocytes, macrophages and polymorphs elicit inflammation.

Some cellular components of the skin immune system

Keratinocytes (p. 9)

Their prime role is to make the protective horny layer (p. 11) and to support to the outermost epithelium of the body but they also have immunological functions in their own right. Keratinocytes produce large numbers of cytokines (see Table 2.2), and can be induced by γ-interferon to express HLA-DR. They can also produce α-melanocyte-stimulating hormone (p. 243), which is immunosuppressive. Keratinocytes play a central part in healing after epidermal injury (Fig. 2.11).

Langerhans cells (p. 12)

These dendritic cells come from the bone marrow and circulate through the epidermis, the dermis, lymphatics (as ‘veiled cells’), and also through the T-cell area of the lymph nodes where they are called ‘dendritic’ or ‘interdigitating’ cells. They can be identified in tissue sections by demonstrating their characteristic surface markers (e.g. CD1a antigen, MHC Class II antigens, adenosine triphosphatase) or S-100 protein in their cytoplasm (also found in melanocytes). Langerhans cells have a key role in antigen presentation.

Dermal dendritic cells

These poorly characterized cells are found around the tiny blood vessels of the papillary dermis. They bear MHC Class II antigens on their surface and,
Helper T cells are divided into type 1 (TH-1) and type 2 lymphocytes (TH-2) according to the main cytokines that they produce (Fig. 2.13). Some skin diseases display a predominantly TH-1 response (e.g. psoriasis), others a mainly TH-2 response (e.g. atopic dermatitis).

**T lymphocytes**

These develop and acquire their antigen receptors (T-cell receptors, TCR) in the thymus. They differentiate into subpopulations, recognizable by their different surface molecules (cluster of differentiation markers), which are functionally distinct.

**T-helper (TH)/inducer cells**

These help B cells to produce antibody and also induce cytotoxic T cells to recognize and kill virally infected cells and allogeneic grafts. TH cells recognize antigen in association with MHC Class II molecules (Fig. 2.12) and, when triggered by antigen, release cytokines that attract and activate other inflammatory cells (see Fig. 2.18). They are CD4+.

**T-cytotoxic (TC) cells**

These lymphocytes are capable of destroying allogeneic and virally infected cells, which they recognize by the MHC Class I molecules on their surface. They are CD8+.

**T-cell receptor and T-cell gene receptor rearrangements**

Most T-cell receptors are composed of an α and β chain, each with a variable (antigen binding) and a constant domain, which are associated with the CD3 cell surface molecules (Fig. 2.12). Many different combinations of separate gene segments, termed V, D and...
J, code for the variable domains of the receptor. An analysis of rearrangements of the gene for the receptor is used to determine whether a T-cell infiltrate is likely to be malignant or reactive. The identification of a specific band, on analysis of DNA from the lesion, which is not matched by the patient’s DNA from other sites, indicates monoclonal T-cell proliferation, and suggests either malignancy or a T-cell response to a single antigen.

L cells/null (non-T, non-B) cells

These leucocytes have properties between those of T and myelomonocytic cells. Most have receptors for FcIgG. This subpopulation contains natural killer (NK) and killer (K) cells.
**Natural killer cells**

These are large granular leucocytes that can kill virally infected cells, or tumour cells that have not previously been sensitized with antibody.

**Killer cells**

These are not a separate cell type, but rather cytotoxic T cells, NK cells or monocytic leucocytes that can kill target cells sensitized with antibody. In antibody-mediated cellular cytotoxicity, antibody binds to antigen on the surface of the target cell: the K cell binds to the antibody at its other (Fc) end by its Fc receptor and the target cell is then lysed.

**Mast cells**

These are present in most connective tissues, predominantly around blood vessels. Their numerous granules contain inflammatory mediators (see Fig. 8.1). In rodents—and probably in humans—there are two distinct populations of mast cells, connective tissue and mucosal, which differ in their staining properties, content of inflammatory mediators and proteolytic enzymes. Skin mast cells play a central part in the pathogenesis of urticaria (p. 94).

**Molecular components of the skin immune system**

**Antigens and haptens**

Antigens are molecules that are recognized by the immune system thereby provoking an immune reaction, usually in the form of a humoral or cell-bound antibody response. Haptens, often chemicals of low molecular weight, cannot provoke an immune reaction themselves unless they combine with a protein. They are important sensitizers in allergic contact dermatitis (p. 80).

**Superantigens**

Some bacterial toxins (e.g. those released by *Staphylococcus aureus*) are prototypic superantigens. Sensitization to such superantigens is not necessary to prime the immune response. Superantigens align with a variety of MHC Class II molecules outside their antigen presentation groove and, without any cellular processing, may directly signal to different classes of T cells within the large family carrying a Vβ type of T-cell receptor (Fig. 2.12). By these means, superantigens can induce massive T-cell proliferation and cytokine production leading to disorders such as the toxic shock syndrome (p. 192). Streptococcal toxins act as superantigens to activate T cells in the pathogenesis of guttate psoriasis.

**Antibodies (immunoglobulins)**

Immunoglobulin G (IgG) is responsible for most of the secondary response to most antigens. It can cross the placenta, and binds complement to activate the classical complement pathway. IgG can coat neutrophils and macrophages (by their FcIgG receptors), and acts as an opsonin by cross-bridging antigen. IgG can also sensitize target cells for destruction by K cells. IgM is the largest immunoglobulin molecule. It is responsible for much of the primary response and, like IgG, it can fix complement but it cannot cross the placenta. IgA is the most common immunoglobulin in secretions. It does not bind complement but can activate complement via the alternative pathway. IgE binds to Fc receptors on mast cells and basophils, where it sensitizes them to release inflammatory mediators in type I immediate hypersensitivity reactions (Fig. 2.14).

**Cytokines**

Cytokines are small proteins secreted by cells such as lymphocytes and macrophages, and also by keratinocytes (Table 2.2). They regulate the amplitude and duration of inflammation by acting locally on nearby cells (paracrine action), on those cells that secreted them (autocrine) and occasionally on distant target cells (endocrine) via the circulation. The term cytokine covers interleukins, interferons, colony-stimulating factors, cytokotxins and growth factors. Interleukins (IL) are produced predominantly by leucocytes, have a known amino acid sequence and are active in inflammation or immunity.

There are many cytokines (Table 2.2), and each may act on more than one type of cell causing many different effects. Cytokines frequently have overlapping actions. In any inflammatory reaction some cytokines...
CHAPTER 2

Fas on epidermal lymphocytes. Interaction of these with Fas ligand on keratinocytes causes e-cadherins to ‘disappear’ leading to intercellular oedema (spongiosis) between desmosomes.

Adhesion molecules

Cellular adhesion molecules (CAMs) are surface glycoproteins that are expressed on many different types of cell; they are involved in cell–cell and cell–matrix adhesion and interactions. CAMs are fundamental in the interaction of lymphocytes with antigen-presenting cells (Fig. 2.12), keratinocytes and endothelial cells and are important in lymphocyte trafficking in the skin during inflammation (Fig. 2.11). CAMs have been classified into four families: cadherins, immunoglobulin superfamily, integrins and selectins. E-cadherins are found on the surface of keratinocytes between the desmosomes. γ-Interferon causes up-regulation of 

Histocompatibility antigens

Like other cells, those in the skin express surface antigens directed by genes of the MHC. The human leucocyte antigen (HLA) region lies on chromosome 6. In particular, HLA-A, -B and -C antigens (the Class I antigens) are expressed on all nucleated cells including keratinocytes, Langerhans cells and cells of the dermis. HLA-DR, -DP, -DQ and -DZ antigens (the Class II antigens) are expressed only on some cells (e.g. Langerhans cells). They are poorly expressed on keratinocytes except during certain reactions (e.g. allergic contact dermatitis) or diseases (e.g. lichen planus). Helper T cells recognize antigens only in the presence of cells bearing Class II antigens. Class II antigens are also important for certain cell–cell interactions. On the other hand, Class I antigens mark target cells for cell-mediated cytotoxic reactions, such as the rejection of skin allografts and the destruction of cells infected by viruses.
Antigen combines with the hand parts of the immunoglobulin (the antigen-binding site or Fab end), the mast cell liberates its mediators into the surrounding tissue. Of these mediators, histamine (from the granules) and leukotrienes (from the cell membrane) induce vasodilatation, and endothelial cells retract allowing transudation into the extravascular space. The vasodilatation causes a pink colour, and the transudation causes swelling. Urticaria and angioedema (p. 94) are examples of immediate hypersensitivity reactions occurring in the skin.

Antigen may be delivered to the skin from the outside (e.g. in a bee sting). This will induce a swelling in everyone by a direct pharmacological action. However, some people, with IgE antibodies against antigens in the venom, swell even more at the site of the sting as the result of a specific immunological reaction. If they are extremely sensitive, they may develop wheezing, wheals and anaphylactic shock (see Fig. 22.5), because of a massive release of histamine into the circulation.

Antigens can also reach mast cells from inside the body. Those who are allergic to shellfish, for example,
may develop urticaria within seconds, minutes or hours of eating one. Antigenic material, absorbed from the gut, passes to tissue mast cells via the circulation, and elicits an urticarial reaction after binding to specific IgE on mast cells in the skin.

Type II: humoral cytotoxic reactions

In the main, these involve IgG and IgM antibodies, which, like IgE, are produced by plasma cells and are present in the interstitial fluid of the skin. When they meet an antigen, they fix and activate complement through a series of enzymatic reactions that generate mediator and cytotoxic proteins. If bacteria enter the skin, IgG and IgM antibodies bind to antigens on them. Complement is activated through the classical pathway, and a number of mediators are generated. Amongst these are the chemotactic factor, C5a, which attracts polymorphs to the area of bacterial invasion, and the opsonin, C3b, which coats the bacteria so that they can be ingested and killed by polymorphs when these arrive (Fig. 2.15). Under certain circumstances, activation of complement can kill cells or organisms directly by the ‘membrane attack complex’ (C5b6789) in the terminal complement pathway. Complement can also be activated by bacteria directly through the alternative pathway; antibody is not required. The bacterial cell wall causes more C3b to be produced by the alternative pathway factors B, D and P (properdin). Aggregated IgA can also activate the alternative pathway.

Activation of either pathway produces C3b, the pivotal component of the complement system. Through the amplification loop, a single reaction can flood the area with C3b, C5a and other amplification loop and terminal pathway components. Complement is the mediator of humoral reactions.

Humoral cytotoxic reactions are typical of defence against infectious agents such as bacteria. However, they are also involved in certain autoimmune diseases such as pemphigoid (Chapter 9).
Occasionally, antibodies bind to the surface of a cell and activate it without causing its death or activating complement. Instead, the cell is stimulated to produce a hormone-like substance that may mediate disease. Pemphigus (Chapter 9) is a blistering disease of skin in which this type of reaction may be important.

**Type III: immune complex-mediated reactions**

Antigen may combine with antibodies near vital tissues so that the ensuing inflammatory response damages them. When an antigen is injected intradermally, it combines with appropriate antibodies on the walls of blood vessels, complement is activated, and polymorphonuclear leucocytes are brought to the area (an Arthus reaction). Degranulation of polymorphs liberates lysosomal enzymes that damage the vessel walls.

Antigen–antibody complexes can also be formed in the circulation, move to the small vessels in the skin and lodge there (Fig. 2.16). Complement will then be activated and inflammatory cells will injure the vessels as in the Arthus reaction. This causes oedema and the extravasation of red blood cells (e.g. the palpable purpura that characterizes vasculitis; Chapter 8).

![Fig. 2.16 Immune complex-mediated vasculitis (type III reaction).](image-url)
cytokines that can injure tissues directly and kill cells or microbes.

**Induction (sensitization) phase** (Fig. 2.17)

When the epidermal barrier is breached, the immune system provides the second line of defence. Among the keratinocytes are Langerhans cells, highly specialized intraepidermal macrophages with tentacles that intertwine among the keratinocytes, providing a net (Fig. 2.7) to ‘catch’ antigens falling down on them from the surface, such as chemicals or the antigens of microbes or tumours. During the initial induction phase, the antigen is trapped by a Langerhans cell which then migrates to the regional lymph node. To do this, it must retract its dendrites and ‘swim upstream’ from the prickle cell layer of the epidermis towards the basement membrane, against the ‘flow’ of keratinocytes generated by the epidermal basal cells. Once in the

**Type IV: cell-mediated immune reactions**

As the name implies, these are mediated by lymphocytes rather than by antibodies. Cell-mediated immune reactions are important in granulomas, delayed hypersensitivity reactions, and allergic contact dermatitis. They probably also play a part in some photosensitive disorders, in protecting against cancer, and in mediating reactions to insect bites.

**Allergic contact dermatitis**

There are two phases: during the induction phase naive lymphocytes become sensitized to a specific antigen; during the elicitation phase antigens entering the skin are processed by antigen-presenting cells such as macrophages and Langerhans cells (Fig. 2.17) and then interact with sensitized lymphocytes. The lymphocytes are stimulated to enlarge, divide and to secrete...
dermis, the Langerhans cell enters the lymphatic system, and by the time it reaches the regional lymph node it will have processed the antigen, which is re-expressed on its surface in conjunction with MHC Class II molecules. In the node, the Langerhans cell mingles with crowds of lymphocytes, where it is most likely to find a T cell with just the right T-cell receptor to bind its now processed antigen. Helper (CD4+) T lymphocytes recognize antigen only in the presence of cells bearing MHC Class II antigens, such as the Langerhans cell. The interactions between surface molecules on a CD4+ T cell and a Langerhans cell are shown in Fig. 2.12. When a T cell interacts with an antigen-presenting cell carrying an antigen to which it can react, the T lymphocyte divides. This division depends upon the persistence of antigen (and the antigen-presenting cells that contain it) and the T-cell growth factor interleukin-2 (IL-2). Eventually, a whole cadre of memory T cells is available to return to the skin to attack the antigen that stimulated their proliferation.

CD4+, CD45+ memory T lymphocytes circulate between nodes and tissues via lymphatic vessels, the thoracic duct, blood and interstitial fluid. They return to the skin aided by ‘homing molecules’ (cutaneous lymphocyte antigen, CLA) that guide their trip so that they preferentially enter the dermis. In the absence of antigen, they merely pass through it, and again enter the lymphatic vessels to return and recirculate. These cells are sentinel cells (Fig. 2.18), alert for their own special antigens. They accumulate in the skin if the host again encounters the antigen that initially

Fig. 2.18 Elicitation phase of allergic contact dermatitis (type IV) reaction.
stimulated their production. This preferential circulation of lymphocytes into the skin is a special part of the ‘skin immune system’ and reflects a selective advantage for the body to circulate lymphocytes that react to skin and skin surface-derived antigens.

**Elicitation (challenge) phase** (Fig. 2.18)

When a T lymphocyte again encounters the antigen to which it is sensitized, it is ready to react. If the antigen is extracellular, as on an invading bacterium, toxin or chemical allergen, the CD4+ T-helper cells do the work. The sequence of antigen processing by the Langerhans cell in the elicitation reaction is similar to the sequence of antigen processing during the induction phase, described above, that leads to the induction of immunity. The antigens get trapped by epidermal Langerhans cells or dermal dendritic cells, which process the antigen intracellularly before re-expressing the modified antigenic determinant on their surfaces. In the elicitation reaction, the Langerhans cells find appropriate T lymphocytes in the dermis, so most antigen presentation occurs there. The antigen is presented to CD4+ T cells which are activated and produce cytokines that cause lymphocytes, polymorphonuclear leucocytes and monocytes in blood vessels to slow as they pass through dermal blood vessels, to stop and emigrate into the dermis causing inflammation (Fig. 2.18). Helper or cytotoxic lymphocytes help to stem the infection or eliminate antigen and polymorphonuclear leucocytes engulf antigens and destroy them. The traffic of inflammatory cells in the epidermis and dermis is determined not only by cytokines produced by lymphocytes, but also by cytokines produced by injured keratinocytes (Fig. 2.11). For example, keratinocyte-derived cytokines can activate Langerhans cells and T cells, and IL-8, produced by keratinocytes, is a potent chemotactic factor for lymphocytes and polymorphs, and brings these up into the epidermis.

**Response to intracellular antigens**

Antigens coming from inside a cell, such as intracellular fungi or viruses and tumour antigens, are presented to cytotoxic T cells (CD8+) by the MHC Class I molecule. Presentation in this manner makes the infected cell liable to destruction by cytotoxic T lymphocytes or K cells. NK cells can also kill such cells, even though they have not been sensitized with antibody.

**Granulomas**

Granulomas form when cell-mediated immunity fails to eliminate antigen. Foreign body granulomas occur because material remains undigested. Immunological granulomas require the persistence of antigen, but the response is augmented by a cell-mediated immune reaction. Lymphokines, released by lymphocytes sensitized to the antigen, cause macrophages to differentiate into epithelioid cells and giant cells. These secrete other cytokines, which influence inflammatory events. Immunological granulomas of the skin are characterized by Langhans giant cells (not to be confused with Langerhans cells; p. 12), epithelioid cells, and a surrounding mantle of lymphocytes.

Granulomatous reactions also occur when organisms cannot be destroyed (e.g. in tuberculosis, leprosy, leishmaniasis), or when a chemical cannot be eliminated (e.g. zirconium or beryllium). Similar reactions are seen in some persistent inflammations of undetermined cause (e.g. rosacea, granuloma annulare, sarcoidosis, and certain forms of panniculitis).

**Further reading**


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**LEARNING POINTS**

1. Many skin disorders are good examples of an immune reaction at work. The more you know about the mechanisms, the more interesting the rashes become.
2. However, the immune system may not be the only culprit. If *Treponema pallidum* had not been discovered, syphilis might still be listed as an autoimmune disorder.
The key to successful treatment is an accurate diagnosis. You can look up treatments, but you cannot look up diagnoses. Without a proper diagnosis, you will be asking ‘What’s a good treatment for scaling feet?’ instead of ‘What’s good for tinea pedis?’ Would you ever ask yourself ‘What’s a good treatment for chest pain?’ Luckily, dermatology differs from other specialties as its diseases can easily be seen. Keen eyes and a magnifying glass are all that are needed for a complete examination of the skin. Sometimes it is best to examine the patient briefly before obtaining a full history: a quick look will often prompt the right questions. However, a careful history is important in every case, as is the intelligent use of the laboratory.

**History**

The key points to be covered in the history are listed in Table 3.1 and should include descriptions of the events surrounding the onset of the skin lesions, of the progression of individual lesions, and of the disease in general, including any responses to treatment. Many patients try a few salves before seeing a physician. Some try all the medications in their medicine cabinets, many of which can aggravate the problem. A careful inquiry into drugs taken for other conditions is often useful. Ask also about previous skin disorders, occupation, hobbies and disorders in the family.

**Examination**

To examine the skin properly, the lighting must be uniform and bright. Daylight is best. The patient should usually undress so that the whole skin can be examined, although sometimes this is neither desirable (e.g. hand warts) nor possible. The presence of a chaperone, ideally a nurse or a relative, is often sensible, and is essential if examination of the genitalia is necessary. Do not be put off this too easily by the elderly, the stubborn, the shy, or the surroundings. Sometimes

---

Table 3.1 Outline of dermatological history.

<table>
<thead>
<tr>
<th>History of present skin condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Site at onset, details of spread</td>
</tr>
<tr>
<td>Itch</td>
</tr>
<tr>
<td>Burning</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Wet, dry, blisters</td>
</tr>
<tr>
<td>Exacerbating factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General health at present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask about fever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Past history of skin disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past general medical history</td>
</tr>
<tr>
<td>Inquire specifically about asthma and hay fever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history of skin disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>If positive— inherited vs. infection/infestation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history of other medical disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social and occupational history</td>
</tr>
<tr>
<td>Hobbies</td>
</tr>
<tr>
<td>Travels abroad</td>
</tr>
<tr>
<td>Relationship of rash to work and holidays</td>
</tr>
<tr>
<td>Alcohol intake</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs used to treat present skin condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
</tr>
<tr>
<td>Systemic</td>
</tr>
<tr>
<td>Physician prescribed</td>
</tr>
<tr>
<td>Patient initiated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs prescribed for other disorders (including those taken before onset of skin disorder)</th>
</tr>
</thead>
</table>
make-up must be washed off or wigs removed. There is nothing more embarrassing than missing the right diagnosis because an important sign has been hidden.

**Distribution**

A dermatological diagnosis is based both on the distribution of lesions and on their morphology and configuration. For example, an area of seborrhoeic dermatitis may look very like an area of atopic dermatitis; but the key to diagnosis lies in the location. Seborrhoeic dermatitis affects the scalp, forehead, eyebrows, nasolabial folds and central chest; atopic dermatitis typically affects the antecubital and popliteal fossae.

See if the skin disease is localized, universal or symmetrical. Depending on the disease suggested by the morphology, you may want to check special areas, like the feet in a patient with hand eczema, or the gluteal cleft in a patient who might have psoriasis. Examine as much of the skin as possible. Look in the mouth and remember to check the hair and the nails (Chapter 13). Note negative as well as positive findings, e.g. the way the shielded areas are spared in a photosensitive dermatitis (see Fig. 16.7). Always keep your eyes open for incidental skin cancers which the patient may have ignored.

**Morphology**

After the distribution has been noted, next define the morphology of the primary lesions. Many skin diseases have a characteristic morphology, but scratching, ulceration and other events can change this. The rule is to find an early or ‘primary’ lesion and to inspect it closely. What is its shape? What is its size? What is its colour? What are its margins like? What are the surface characteristics? What does it feel like?

Most types of primary lesion have one name if small, and a different one if large. The scheme is summarized in Table 3.2.

<table>
<thead>
<tr>
<th>Terminology of primary lesions.</th>
<th>Small (&lt; 0.5 cm)</th>
<th>Large (&gt; 0.5 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated solid lesion</td>
<td>Papule</td>
<td>Nodule (&gt; 0.5 cm in both width and depth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plaque (&gt; 2 cm in width but without substantial depth)</td>
</tr>
<tr>
<td>Flat area of altered colour or texture</td>
<td>Macule</td>
<td>Large macule (patch)</td>
</tr>
<tr>
<td>Fluid-filled blister</td>
<td>Vesicle</td>
<td>Bulla</td>
</tr>
<tr>
<td>Pus-filled lesion</td>
<td>Pustule</td>
<td>Abscess</td>
</tr>
<tr>
<td>Extravasation of blood into skin</td>
<td>Petechia (pinhead size)</td>
<td>Ecchymosis</td>
</tr>
<tr>
<td></td>
<td>Purpura (up to 2 mm in diameter)</td>
<td>Haematoma</td>
</tr>
<tr>
<td>Accumulation of dermal oedema</td>
<td>Wheal (can be any size)</td>
<td>Angioedema</td>
</tr>
</tbody>
</table>

**Terminology of lesions** (Fig. 3.1)

**Primary lesions**

*Erythema* is redness caused by vascular dilatation.

A *papule* is a small solid elevation of skin, less than 0.5 cm in diameter.

A *plaque* is an elevated area of skin greater than 2 cm in diameter but without substantial depth.
A **macule** is a small flat area of altered colour or texture.

A **vesicle** is a circumscribed elevation of skin, less than 0.5 cm in diameter, and containing fluid.

A **bulla** is a circumscribed elevation of skin over 0.5 cm in diameter and containing fluid.

A **pustule** is a visible accumulation of pus in the skin.

An **abscess** is a localized collection of pus in a cavity, more than 1 cm in diameter. Abscesses are usually nodules, and the term ‘purulent bulla’ is sometimes used to describe a pus-filled blister that is situated on top of the skin rather than within it.

A **wheal** is an elevated white compressible evanescent area produced by dermal oedema. It is often surrounded by a red axon-mediated flare. Although usually less than 2 cm in diameter, some wheals are huge.

**Angioedema** is a diffuse swelling caused by oedema extending to the subcutaneous tissue.

---

**Fig. 3.1** Terminology of skin lesions.
A **nodule** is a solid mass in the skin, usually greater than 0.5 cm in diameter, in both width and depth, which can be seen to be elevated or can be palpated.

A **tumour** is harder to define as the term is based more correctly on microscopic pathology than on clinical morphology. We keep it here as a convenient term to describe an enlargement of the tissues by normal or pathological material or cells that form a mass, usually more than 1 cm in diameter. Because the word ‘tumour’ can scare patients, tumours may courteously be called ‘large nodules’, especially if they are not malignant.

A **papilloma** is a nipple-like projection from the skin.

**Petechiae** are pinhead-sized macules of blood in the skin.

The term **purpura** describes a larger macule or papule of blood in the skin. Such blood-filled lesions do not blanch if a glass lens is pushed against them (diascopy).

An **echymosis** is a larger extravasation of blood into the skin.

A **haematoma** is a swelling from gross bleeding.

A **burrow** is a linear or curvilinear papule, with some scaling, caused by a scabies mite.

A **comedo** is a plug of greasy keratin wedged in a dilated pilosebaceous orifice. Open comedones are blackheads. The follicle opening of a closed comedo is nearly covered over by skin so that it looks like a pinhead-sized, ivory-coloured papule.

**Telangiectasia** is the visible dilatation of small cutaneous blood vessels.

**Poikiloderma** is a combination of atrophy, reticulate hyperpigmentation and telangiectasia.

### Secondary lesions

These evolve from primary lesions.

A **scale** is a flake arising from the horny layer.

A **keratosis** is a horn-like thickening of the stratum corneum.

A **crust** may look like a scale, but is composed of dried blood or tissue fluid.

An **ulcer** is an area of skin from which the whole of the epidermis and at least the upper part of the dermis has been lost. Ulcers may extend into subcutaneous fat, and heal with scarring.

An **erosion** is an area of skin denuded by a complete or partial loss of only the epidermis. Erosions heal without scarring.

An **excoriation** is an ulcer or erosion produced by scratching.

A **fissure** is a slit in the skin.

A **sinus** is a cavity or channel that permits the escape of pus or fluid.

A **scar** is a result of healing, where normal structures are permanently replaced by fibrous tissue.

**Atrophy** is a thinning of skin caused by diminution of the epidermis, dermis or subcutaneous fat. When the epidermis is atrophic it may crinkle like cigarette paper, appear thin and translucent, and lose normal surface markings. Blood vessels may be easy to see in both epidermal and dermal atrophy.

**Lichenification** is an area of thickened skin with increased markings.

A **stria** (stretch mark) is a streak-like linear atrophic pink, purple or white lesion of the skin caused by changes in the connective tissue.

**Pigmentation**, either more or less than surrounding skin, can develop after lesions heal.

Having identified the lesions as primary or secondary, adjectives can be used to describe them in terms of their other features.

- **Colour** (e.g. salmon-pink, lilac, violet).
- **Sharpness of edge** (e.g. well-defined, ill-defined).
- **Surface contour** (e.g. dome-shaped, umbilicated, spire-like; Fig. 3.2).
- **Geometric shape** (e.g. nummular, oval, irregular, like the coast of Maine).
- **Texture** (e.g. rough, silky, smooth, hard).
- **Smell** (e.g. foul-smelling).
- **Temperature** (e.g. hot, warm).

Dermatologists also use a few special adjectives which warrant definition.

- **Nummular** means round or coin-like.
- **Annular** means ring-like.
- **Circinate** means circular.
- **Arcuate** means curved.
- **Discoid** means disc-like.
- **Gyrate** means wave-like.
- **Retiform and reticulate** mean net-like.

To describe a skin lesion, use the term for the primary lesion as the noun, and the adjectives mentioned above to define it. For example, the lesions of psoriasis may appear as ‘salmon-pink sharply demarcated nummular plaques covered by large silver polygonal scales’.

Try not to use the terms ‘lesion’ or ‘area’. Why say ‘papular lesion’ when you can say papule? It is
almost as bad as the ubiquitous term ‘skin rash’. By the way, there are very few diseases that are truly ‘maculopapular’. The term is best avoided except to describe some drug eruptions and viral exanthems. Even then, the terms ‘scarlatiniform’ (like scarlet fever —punctate, slightly elevated papules) or ‘morbilliform’ (like measles—a net-like blotchy slightly elevated pink exanthem) are more helpful.

**Configuration**

After unravelling the primary and secondary lesions, look for arrangements and configurations that can be, for example, discrete, confluent, grouped, annular, arcuate or dermatomal (Fig. 3.3). Note that while individual lesions may be annular, several individual lesions may arrange themselves into an annular configuration. Terms like annular, and other adjectives discussed under the morphology of individual lesions, can apply to their groupings too. The Köbner or isomorphic phenomenon is the induction of skin lesions by, and at the site of, trauma such as scratch marks or operative incisions.

**Special tools and techniques**

A **magnifying lens** is a helpful aid to diagnosis because subtle changes in the skin become more apparent when enlarged. One attached to spectacles will leave your hand free.

A Wood’s light, emitting long wavelength ultraviolet radiation, will help with the examination of some skin conditions. Fluorescence is seen in some fungal infections (Chapter 14), erythrasma (p. 189) and pseudomonas infections. Some subtle disorders of pigmentation can be seen more clearly under Wood’s light, e.g. the pale patches of tuberous sclerosis, low-grade vitiligo and pityriasis versicolor, and the darker café-au-lait patches of neurofibromatosis. The urine in hepatic cutaneous porphyria (p. 287) often fluoresces coral pink, even without solvent extraction of the porphyrins (see Fig. 19.10).

**Diascopy** is the name given to the technique in which a glass slide or clear plastic spoon is used to blanch vascular lesions and so to unmask their underlying colour.

**Photography**, conventional or digital, helps to record the baseline appearance of a lesion or rash, so that change can be assessed objectively at later visits. Small changes in pigmented lesions can be detected by analysing sequential digital images stored in computerized systems.

**Dermatoscopy (epiluminescence microscopy, skin surface microscopy)**

This non-invasive technique for diagnosing pigmented lesions in vivo has come of age in the last few years. It is particularly useful in the diagnosis of malignant melanomas. The lesion is covered with mineral oil, alcohol or water and then illuminated and observed at
Assessment

Next try to put the disease into a general class; the titles of the chapters in this book are representative. Once classified, a differential diagnosis is usually forthcoming. Each diagnosis can then be considered on its merits, and laboratory tests may be used to confirm or refute diagnoses in the differential list. At this stage you must make a working diagnosis or formulate a plan to do so!

LEARNING POINTS

1. As Osler said: ‘See and then reason, but see first’.
2. A correct diagnosis is the key to correct treatment.
3. The term ‘skin rash’ is as bad as ‘gastric stomach’.
4. Avoid using too many long Latin descriptive names as a cloak for ignorance.
5. The history is especially important when the diagnosis is difficult.
6. Undress the patients and use a lens, even if it only gives you more time to think.
7. Remember the old adage that if you do not look in the mouth you will put your foot in it.

Chapter 3

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Side-room and office tests

A number of tests can be performed in the practice office so that their results will be available immediately.

Potassium hydroxide preparations for fungal infections

If a fungal infection is suspected, scales or plucked hairs can be dissolved in an aqueous solution of 20% potassium hydroxide (KOH) containing 40% dimethyl sulphoxide (DMSO). The scale from the edge of a scaling lesion is vigorously scraped on to a glass slide with a No. 15 scalpel blade or the edge of a second glass slide. Other samples can include nail clippings, the roofs of blisters, hair pluckings, and the contents of pustules when a candidial infection is suspected. A drop or two of the KOH solution is run under the cover slip (Fig. 3.6). After 5–10 min the mount is examined under a microscope with the condenser lens lowered to increase contrast. Nail clippings take longer to clear—up to a couple of hours. With experience, fungal and candidal hyphae can be readily detected (Fig. 3.7). No heat is required if DMSO is included in the KOH solution.

Detection of a scabies mite

Burrows in an itchy patient are diagnostic of scabies. Retrieving a mite from the skin will confirm the diagnosis and convince a sceptical patient of the infestation. The burrow should be examined under a magnifying glass; the acarus is seen as a tiny black or grey dot at the most recent, least scaly end. It can be removed by a sterile needle and placed on a slide within a marked circle. Alternatively, if mites are not seen, possible burrows can be vigorously scraped with a No. 15 scalpel blade, moistened with liquid paraffin or vegetable oil, and the scrapings transferred to a slide. Patients never argue the toss when confronted by a magnified mobile mite. Dermatoscopy (see above) can also be used to detect the scabies mite.

Cytology (Tzanck smear)

Cytology can aid diagnosis of viral infections such as herpes simplex and zoster, and of bullous diseases such as pemphigus. A blister roof is removed and the cells from the base of the blister are scraped off with a No. 10 or 15 surgical blade. These cells are smeared on to a microscope slide, air-dried and fixed with methanol. They are then stained with Giemsa, toluidine blue or Wright’s stain. Acantholytic cells (Chapter 9) are seen in pemphigus and multinucleate giant cells are diagnostic of herpes simplex or varicella zoster infections (Chapter 14). Practice is needed to get good preparations. The technique remains popular in the USA but has fallen out of favour in the UK as histology, virological culture and electron microscopy have become more accessible.

Patch tests

Patch tests are invaluable in detecting the allergens responsible for allergic contact dermatitis (Chapter 7).
Prick testing

Prick testing is much less helpful in dermatology. It detects immediate (type I) hypersensitivity (Chapter 2) and patients should not have taken systemic antihistamines for at least 48 h before the test. Commercially prepared diluted antigens and a control are placed as single drops on marked areas of the forearm. The skin is gently pricked through the drops using separate sterile fine (e.g. Size 25 gauge, or smaller) needles. The prick should not cause bleeding. The drops are then removed with a tissue wipe. After 10 min the sites are inspected and the diameter of any wheal measured and recorded. A result is considered positive if the test antigen causes a wheal of 4 mm or greater (Fig. 3.10) and the control elicits negligible reaction. Like patch testing, prick testing should not be undertaken by those without formal training in the procedure. Although the risk of anaphylaxis is small, resuscitation facilities including adrenaline (epinephrine) and oxygen (p. 310) must be available. The relevance of positive results to the cause of the condition under investigation—usually urticaria or atopic dermatitis—is often debatable. Positive results should correlate with positive radioallergosorbent tests (RAST; p. 74) used to measure total and specific immunoglobulin E (IgE) levels to
Local anaesthetic

Lignocaine (lidocaine) 1–2% is used. Sometimes adrenaline 1:200,000 is added. This causes vasoconstriction, reduced clearance of the local anaesthetic and prolongation of the local anaesthetic effect. Plain lignocaine should be used on the fingers, toes and penis as the prolonged vasoconstriction produced by adrenaline can be dangerous here. Adrenaline is also best avoided in diabetics with small vessel disease, in those with a history of heart disease (including dysrhythmias), in patients taking non-selective α blockers and tricyclic antidepressants (because of potential interactions) and in uncontrolled hyperthyroidism. There are exceptions to these general rules and, undoubtedly, the total dose of local anaesthetic and/or adrenaline is important. Nevertheless, the rules should not be broken unless the surgeon is quite sure that the procedure that he or she is about to embark on is safe.

It is wise to avoid local anaesthesia during early pregnancy and to delay non-urgent procedures until after the first trimester.

As ‘B’ follows ‘A’ in the alphabet, get into the habit of checking the precise concentration of the lignocaine ± added adrenaline on the label before withdrawing it into the syringe and then, before injecting it, confirm that the patient has not had any previous allergic reactions to local anaesthetic.

Skin biopsy

Biopsy (from the Greek bios meaning ‘life’ and opsis ‘sight’) of skin lesions is useful to establish or confirm a clinical diagnosis. A piece of tissue is removed surgically for histological examination and, sometimes, for other tests (e.g. culture for organisms). When used selectively, a skin biopsy can solve the most perplexing problem but, conversely, will be unhelpful in conditions without a specific histology (e.g. most drug eruptions, pityriasis rosea, reactive erythemas).

Skin biopsies may be incisional, when just part of a lesion is removed for laboratory examination or excisional, when the whole lesion is cut out. Excisional biopsy is preferable for most small lesions (up to 0.5 cm diameter) but incisional biopsy is chosen when the partial removal of a larger lesion is adequate for diagnosis, and complete removal might leave an unnecessary and unsightly scar. Ideally, an incisional biopsy should include a piece of the surrounding normal skin (Fig. 3.11) although this may not be possible if a small punch is used.

The main steps in skin biopsy are:
1. administration of local anaesthesia; and
2. removal of all (excision) or part (incision) of the lesion and repair of the defect made by a scalpel or punch.

Infiltration of the local anaesthetic into the skin around the area to be biopsied is the most widely used method. If the local anaesthetic is injected into the subcutaneous fat, it will be relatively pain-free, will produce a diffuse swelling of the skin and will take several minutes to induce anaesthesia. Intradermal injections are painful and produce a discrete wheal associated with rapid anaesthesia. The application of EMLA cream (eutectic mixture of local anaesthesia) to the operation site 2 h before giving a local anaesthetic to children helps to numb the initial prick.

Scalpel biopsy

This provides more tissue than a punch biopsy. It can be used routinely, but is especially useful for biopsying disorders of the subcutaneous fat, for obtaining specimens with both normal and abnormal skin for comparison (Fig. 3.11) and for removing small lesions in toto (excision biopsy, see p. 321). After selecting the lesion for biopsy, an elliptical piece of skin is excised.
first, and a cylinder of skin is incised with the punch by rotating it back and forth (Fig. 3.12). Skin is lifted up carefully with a needle or forceps and the base is cut off at the level of subcutaneous fat. The defect is cauterized or repaired with a single suture. The biopsy specimen must not be crushed with the forceps or critical histological patterns may be distorted.

The tissue can be sent to the pathologist with a summary of the history, a differential diagnosis and the patient’s age. Close liaison with the pathologist is essential, because the diagnosis may only become apparent with knowledge of both the clinical and histological features.

Table 3.3 Guidelines for skin biopsies.

<table>
<thead>
<tr>
<th>Sample a fresh lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain your specimen from near the lesion’s edge</td>
</tr>
<tr>
<td>Avoid sites where a scar would be conspicuous</td>
</tr>
<tr>
<td>Avoid the upper trunk or jaw line where keloids are most likely to form</td>
</tr>
<tr>
<td>Avoid the legs, where healing is slow</td>
</tr>
<tr>
<td>Avoid lesions over bony prominences, where infection is more likely</td>
</tr>
<tr>
<td>Use the scalpel technique for scalp disorders and diseases of the subcutaneous fat or vessels</td>
</tr>
<tr>
<td>Do not crush the tissue</td>
</tr>
<tr>
<td>Place in proper fixative</td>
</tr>
<tr>
<td>If two lesions are sampled, be sure they do not get mixed up or mislabelled. Label specimen containers before the biopsy is placed in them</td>
</tr>
<tr>
<td>Make sure that the patient’s name, age and sex are clearly indicated on the pathology form</td>
</tr>
<tr>
<td>Provide the pathologist with a legible summary of the history, the site of the biopsy and a differential diagnosis</td>
</tr>
<tr>
<td>Discuss the results with the pathologist</td>
</tr>
</tbody>
</table>

Punch biopsy

The skin is sampled with a small (3–4 mm diameter) tissue punch. Lignocaine 1% is injected intradermally first, and a cylinder of skin is incised with the punch by rotating it back and forth (Fig. 3.12). Skin is lifted up carefully with a needle or forceps and the base is cut off at the level of subcutaneous fat. The defect is cauterized or repaired with a single suture. The biopsy specimen must not be crushed with the forceps or critical histological patterns may be distorted.

The tissue can be sent to the pathologist with a summary of the history, a differential diagnosis and the patient’s age. Close liaison with the pathologist is essential, because the diagnosis may only become apparent with knowledge of both the clinical and histological features.

Fig. 3.11 Incision biopsy. This should include adjacent normal skin.

The specimen should include the subcutaneous fat. Removing the specimen with forceps may cause crush artefact, which can be avoided by lifting the specimen with either a Gillies hook or a syringe needle. The wound is then sutured; firm compression for 5 min stops oozing. Non-absorbable 3/0 sutures are used for biopsies on the legs and back, 5/0 for the face, and 4/0 for elsewhere. Stitches are usually removed from the face in 4 days, from the anterior trunk and arms in 7 days, and from the back and legs in 10 days. Some guidelines for skin biopsies are listed in Table 3.3.

Fig. 3.12 Steps in taking a punch biopsy.
Clinical dermatology is a visual specialty. You must see the disease, and understand what you are seeing. Look closely and thoroughly. Take time. Examine the whole body. Locate primary lesions and check configuration and distribution. Ask appropriate questions, especially if the diagnosis is difficult. Classify the disorder and list the differential diagnoses. Use the history, examination and laboratory tests to make a diagnosis.
LEARNING POINTS

1. A biopsy is the refuge of a bankrupt mind when dealing with conditions that do not have a specific histology. Here, a return to the history and examination is more likely to reveal diagnostic clues than a pathologist.
2. If you do not remember the two essential checks before injecting local anaesthetic then read p. 37 again.

Further reading


if this cannot be made by clinical features alone. Then treat. Refer the patient to a dermatologist if:
- you cannot make a diagnosis;
- the disorder does not respond to treatment;
- the disorder is unusual or severe; or
- you are just not sure.
The complex but orderly processes of keratinization, and of cell cohesion and proliferation within the epidermis, have been described in Chapter 2. As they proceed, the living keratinocytes of the deeper epidermis change into the dead corneocytes of the horny layer, where they are stuck together by intercellular lipids. They are then shed in such a way that the surface of the normal skin does not seem scaly to the naked eye. Shedding balances production, so that the thickness of the horny layer does not alter. However, if keratinization or cell cohesion is abnormal, the horny layer may become thick or the skin surface may become dry and scaly. Such changes can be localized or generalized.

In this chapter we describe a variety of skin disorders that have as their basis a disorder of keratinization. During the last few years the molecular mechanisms underlying many of these have become clearer, including abnormal genetic coding for keratins, the enzymes involved in cell cohesion in the horny layer, and the molecules that are critical in the signalling pathway governing cell cohesion in the spinous layer.

The ichthyoses

The word ichthyosis comes from the Greek word for a fish. It is applied to disorders that share, as their main feature, a dry rough skin with marked scaling but no inflammation. Strictly speaking, the scales lack the regular overlapping pattern of fish scales, but the term is usefully descriptive and too well entrenched to be discarded. There are several types.

**Ichthyosis vulgaris**

**Cause**

Inherited as an autosomal dominant disorder, this condition is common and affects about 1 person in 300. The relevant gene may be concerned with the production of profilaggrin, a precursor of filaggrin, itself a component of keratohyalin granules.

**Presentation**

The dryness is usually mild and symptoms are few. The scales are small and branny, being most obvious on the limbs and least obvious in the major flexures. The skin creases of the palm may be accentuated. Keratosis pilaris (p. 44) is often present on the limbs.

**Clinical course**

The skin changes are not usually present at birth but develop over the first few years of life. Some patients improve in adult life, particularly during warm weather, but the condition seldom clears completely.

**Complications**

The already dry skin chaps in the winter and is easily irritated by degreasing agents. This should be taken into account in the choice of a career. Ichthyosis of this type is apt to appear in a stubborn combination with atopic eczema.

**Differential diagnosis**

It can usually be distinguished from less common types of ichthyosis on the basis of the pattern of inheritance and of the type and distribution of the scaling.
Investigations
None are usually needed.

Treatment
This is palliative. The dryness can be helped by the regular use of emollients, which are best applied after a shower or bath. Emulsifying ointment, soft white paraffin, E45 and unguentum merck are all quite suitable (Formulary 1, p. 328) and the selection depends on the patient’s preference. Many find proprietary bath oils and creams containing urea or lactic acid helpful also (Formulary 1, p. 331).

X-linked recessive ichthyosis

Cause
This less common type of ichthyosis is inherited as an X-linked recessive trait and therefore, in its complete form, is seen only in males, although some female carriers show mild scaling. The condition affects about 1 in 6000 males in the UK and is associated with a deficiency of the enzyme steroid sulphatase, which hydrolyses cholesterol sulphate. The responsible gene has been localized to the terminal part of the X chromosome at Xp 22.3 (see Chapter 21).

Presentation and course
In contrast to the delayed onset of the dominantly inherited ichthyosis vulgaris, scaling appears early, often soon after birth, and always by the first birthday. The scales are larger and browner (Fig. 4.1), involve the neck, and to a lesser extent the popliteal and antecubital areas, as well as the skin generally. The palms and soles are normal. There is no association with atopy or keratosis pilaris. The condition persists throughout life.

Complications
Corneal opacities may appear in adult life. Kallmann’s syndrome is caused by the deletion of a part of the X chromosome that includes the gene for X-linked recessive ichthyosis, which is therefore one of its features. Other features of this contiguous gene disorder are hypogonadism, anosmia and neurological defects.

Fig. 4.1 Ichthyosis: large rather dark scales suggest the less common type inherited as a sex-linked recessive trait.

Differential diagnosis
This is as for ichthyosis vulgaris. It is helpful to remember that only males are affected. Bear Kallmann’s syndrome in mind if there are other congenital abnormalities.

Investigations
None are usually needed. A few centres can measure steroid sulphatase in fibroblasts cultured from a skin biopsy.

Treatment
Oral aromatic retinoids are probably best avoided. Topical measures are as for ichthyosis vulgaris.

Collodion baby (Fig. 4.2)
This is a description and not a diagnosis. The bizarre skin charges are seen at birth. At first the stratum corneum is smooth and shiny, and the skin looks as though it has been covered with cellophane or collodion. Its tightness may cause ectropion and feeding difficulties. The shiny outer surface is shed within a few days leaving behind, most often, a non-bullous
becomes generally red and shows numerous blisters. The redness fades over a few months, and the tendency to blister also lessens, but during childhood a gross brownish warty hyperkeratosis appears, sometimes in a roughly linear form and usually worst in the flexures. The histology is distinctive: a thickened granular cell layer contains large granules, and clefts may be seen in the upper epidermis. The condition is caused by mutations in the genes (on chromosomes 12q13 and 17q21) controlling the production of keratins 1 and 10. A few patients with localized areas of hyperkeratosis with the same histological features have gonadal mosaicism, and so their children are at risk of developing the generalized form of the disorder. Treatment is symptomatic and antibiotics may be needed if the blisters become infected. Acitretin (Formulary 2, p. 349) has helped in severe cases.

Other ichthyosiform disorders

Sometimes ichthyotic skin changes are a minor part of a multisystem disease, but such associations are very rare. Refsum’s syndrome, an autosomal recessive trait, is caused by deficiency of a single enzyme concerned in the breakdown of phytanic acid, which then accumulates in the tissues. The other features (retinal degeneration, peripheral neuropathy and ataxia) overshadow the minor dryness of the skin.

Rud’s syndrome is an ichthyosiform erythroderma in association with mental retardation and epilepsy. In Netherton’s syndrome, brittle hairs, with a so-called ‘bamboo deformity’, are present as well as a curious gyrate and erythematous hyperkeratotic eruption (ichthyosis circumflexa). Other conditions are identified by confusing acronyms: IBIDS (also known as trichothiodystrophy) stands for Ichthyosis, Brittle hair, Impaired intelligence, Decreased fertility and Short stature; the KID syndrome consists of Keratitis, Ichthyosis and Deafness.

Acquired ichthyosis

It is unusual for ichthyosis to appear for the first time in adult life; but if it does, an underlying disease should be suspected. The most frequent is Hodgkin’s disease. Other recorded causes include other lymphomas, leprosy, sarcoidosis, malabsorption and a poor diet. The skin may also appear dry in hypothyroidism.
Other disorders of keratinization

Keratosis pilaris

Cause
This common condition is inherited as an autosomal dominant trait, and is possibly caused by mutations in a gene lying on the short arm of chromosome 18. The abnormality lies in the keratinization of hair follicles, which become filled with horny plugs.

Presentation and course
The changes begin in childhood and tend to become less obvious in adult life. In the most common type, the greyish horny follicular plugs, sometimes with red areolae, are confined to the outer aspects of the thighs and upper arms, where the skin feels rough. Less often the plugs affect the sides of the face; perifollicular erythema and loss of eyebrow hairs may then occur. There is an association with ichthyosis vulgaris.

Complications
Involvement of the cheeks may lead to an ugly pitted scarring. Rarely, the follicles in the eyebrows may be damaged with subsequent loss of hair there.

Differential diagnosis
A rather similar pattern of widespread follicular keratosis (phrynoderma) can occur in severe vitamin deficiency. The lack is probably not just of vitamin A, as was once thought, but of several vitamins.

Investigations
None are needed.

Treatment
Treatment is not usually needed, although keratolytics such as salicylic acid or urea in a cream base may smooth the skin temporarily (Formulary 1, p. 331).

Keratosis follicularis (Darier’s disease)

Cause
This rare condition is inherited as an autosomal dominant trait. Fertility tends to be low and many cases represent new mutations. The abnormal gene (on chromosome 12q23-q24.1) encodes for a molecule important in a signalling pathway that regulates cell–cell adhesion in the epidermis.

Presentation
The first signs usually appear in the mid-teens, sometimes after overexposure to sunlight. The characteristic lesions are small pink or brownish papules with a greasy scale (Fig. 4.3). These coalesce into warty plaques in a ‘seborrhoeic’ distribution (Fig. 4.4). Early lesions are often seen on the sternal and interscapular areas, and behind the ears. The severity of the condition varies greatly from person to person: sometimes the skin is widely affected. The abnormalities remain for life, often causing much embarrassment and discomfort.

Other changes include lesions looking like plane warts on the backs of the hands, punctate keratoses or...
Differential diagnosis

The distribution of the lesions may be similar to that of seborrhoeic eczema, but this lacks the warty papules of Darier’s disease. The distribution differs from that of acanthosis nigricans (mainly flexural) and of keratosis pilaris (favours the outer upper arms and thighs). Other forms of folliculitis and Grover’s disease (p. 111) can also cause confusion.

Investigations

The diagnosis should be confirmed by a skin biopsy, which will show characteristic clefts in the epidermis, and dyskeratotic cells.

Treatment

Severe and disabling disease can be dramatically alleviated by long-term acitretin (Formulary 2, p. 349). Milder cases need only topical keratolytics, such as salicylic acid, and the control of local infection (Formulary 1, p. 334).

Keratoderma of the palms and soles

Inherited types

Many genodermatoses share keratoderma of the palms and soles as their main feature; they are not described in detail here. The clinical patterns and modes of inheritance vary from family to family. Punctate, striate, diffuse and mutilating varieties have been documented, sometimes in association with metabolic disorders such as tyrosinaemia, or with changes elsewhere. The punctate type is caused by mutations in the keratin 16 gene on chromosome 17q12-q21; the epidermolytic type by mutations in the gene for keratin 9, found only on palms and soles.

The most common pattern is a diffuse one, known also as tylosis (Fig. 4.6), which is inherited as an autosomal dominant trait. In a few families these changes have been associated with carcinoma of the oesophagus, but in most families this is not the case.

Treatment tends to be unsatisfactory, but keratolytics such as salicylic acid and urea can be used in higher concentrations on the palms and soles than elsewhere (Formulary 1, p. 331).
time of the menopause. It is most marked around the borders of the heels where painful fissures form and interfere with walking (Fig. 4.7). Regular paring and the use of keratolytic ointments are often more helpful than attempts at hormone replacement, and the condition tends to settle over a few years. Acitretin in low doses may be worth a trial.

Knuckle pads

Cause

Sometimes these are familial; usually they are not. Trauma seems not to be important.

Presentation

Fibromatous and hyperkeratotic areas appear on the backs of many finger joints, usually beginning in late childhood and persisting thereafter. There may be an association with Dupuytren’s contracture.

Differential diagnosis

Occupational callosities, granuloma annulare and viral warts should be considered.

Investigations

A biopsy may be helpful in the few cases of genuine clinical difficulty.

Treatment

None, including surgery, is satisfactory.

Callosities and corns

Both are responses to pressure. A callosity is a more diffuse type of thickening of the keratin layer, which seems to be a protective response to widely applied repeated friction or pressure. Callosities are often occupational; e.g. they are seen on the hands of manual workers. Usually painless, they need no therapy.

Corns have a central core of hard keratin, which can hurt if forced inwards. They appear where there is high local pressure, often between bony prominences and shoes. Favourite areas include the backs of the toe.
joints, and the soles under prominent metatarsals. ‘Soft corns’ arise in the third or fourth toe clefts when the toes are squeezed together by tight shoes; such corns are often macerated.

The main differential is from hyperkeratotic warts, but these will show tiny bleeding points when pared down, whereas a corn has only its hard compacted avascular core surrounded by a more diffuse thickening of opalescent keratin.

The right treatment for corns is to eliminate the pressure that caused them, but patients may be slow to accept this. While regular paring reduces the symptoms temporarily, well-fitting shoes are essential. Corns under the metatarsals can be helped by soft spongy soles, but sometimes need orthopaedic alteration of weight bearing. Special care is needed with corns on ischaemic or diabetic feet, which are at greater risk of infection and ulceration.

Further reading


One to three per cent of most populations have psoriasis, which is most prevalent in European and North American white people, uncommon in American black people and almost non-existent in American Indians. It is a chronic non-infectious inflammatory skin disorder, characterized by well-defined erythematous plaques bearing large adherent silvery scales. It can start at any age but is rare under 10 years, and appears most often between 15 and 40 years. Its course is unpredictable but is usually chronic with exacerbations and remissions.

Cause and Pathogenesis

The precise cause of psoriasis is still unknown. However, there is often a genetic predisposition, and sometimes an obvious environmental trigger.

There are two key abnormalities in a psoriatic plaque: hyperproliferation of keratinocytes; and an inflammatory cell infiltrate in which neutrophils and TH-1 type T lymphocytes predominate. Each of these abnormalities can induce the other, leading to a vicious cycle of keratinocyte proliferation and inflammatory reaction; but it is still not clear which is the primary defect. Perhaps the genetic abnormality leads first to keratinocyte hyperproliferation that, in turn, produces a defective skin barrier (p. 11) allowing the penetration by, or unmasking of, hidden antigens to which an immune response is mounted. Alternatively, the psoriatic plaque might reflect a genetically determined reaction to different types of trauma (e.g. physical wounds, environmental irritants and drugs) in which the healing response is exaggerated and uncontrolled.

To prove the primary role of an immune reaction, putative antigens (e.g. bacteria, viruses or autoantigens) that initiate the immune response will have to be identified. This theory postulates that the increase in keratinocyte proliferation is caused by inflammatory cell mediators or signalling. Theories about the pathogenesis of psoriasis tend to tag along behind fashions in cell biology, and this idea is currently in vogue.

Genetics

A child with one affected parent has a 16% chance of developing the disease, and this rises to 50% if both parents are affected. Genomic imprinting (p. 301) may explain why psoriatic fathers are more likely to pass on the disease to their children than are psoriatic mothers. If non-psoriatic parents have a child with psoriasis, the risk for subsequent children is about 10%. In one study, the disorder was concordant in 70% of monozygotic twins but in only 20% of dizygotic ones. These figures are useful for counselling but psoriasis does not usually follow a simple Mendelian pattern of inheritance. The mode of inheritance has therefore to be categorized as genetically complex, implying a polygenic inheritance.

Psoriasis is also genetically heterogeneous. Early onset psoriasis shows an obvious hereditary element and linkage analysis (p. 300) revealed the first psoriasis susceptibility locus (S1), on 6p—close to the major histocompatibility complex Class I (MHC-I) region, but probably not HLA-C itself. The risk of those with the HLA-CW6 genotype developing psoriasis is 20 times that of those without it; 10% of CW6+ individuals will develop psoriasis. Other MHC-I associated diseases include Behçet’s disease, ulcerative colitis and anterior uveitis. Interestingly, T-cell mediation is also seen in these diseases. The hereditary element and the HLA associations are much weaker in late-onset psoriasis.
In 1994, a second psoriasis susceptibility locus (S2) was discovered on 17q, incidentally next to a Crohn’s disease susceptibility gene. Since then three more susceptibility loci have been confirmed (on 4q, 1q and 3q) and a few more await verification. It is unlikely to be coincidental that two of these loci (6p.21 and 1q.21–23) include genes that encode enzymes involved in cornification (p. 10).

This large number of genetic linkages suggests that ‘psoriasis’ may in fact be a phenotypic expression of several different genetic aberrations, all characterized by well-defined erythematous and scaly plaques, which are clinically indistinguishable. This idea fits the view that psoriasis is a multifactorial disease with a complex genetic trait, and that an individual’s predisposition to it is determined by a large number of genes, each of which has only a low penetrance. Clinical expression of the disease is brought about by subsequent environmental stimuli.

**Epidermal cell kinetics**

The increased epidermal proliferation of psoriasis is caused by an excessive number of germinative cells entering the cell cycle rather than by a decrease in cell cycle time. The growth fraction (p. 8) approaches 100%, compared with 30% in normal skin. The epidermal turnover time (p. 8) is greatly shortened, to less than 10 days as compared with 60 days in normal skin. This epidermal hyperproliferation accounts for many of the metabolic abnormalities associated with psoriasis. It is not confined to obvious plaques: similar but less marked changes occur in the apparently normal skin of psoriatics as well.

The exact mechanism underlying this increased epidermal proliferation is uncertain. Cyclic guanosine monophosphate (cGMP), arachidonic acid metabolites, polyamines, calmodulin and plasminogen activator are all increased in psoriatic plaques but theories based on their prime involvement have neither stood the test of time nor provided useful targets for therapeutic intervention. Perhaps the underlying abnormality is a genetic defect in the control of keratinocyte growth. γ-Interferon (IFN-γ) inhibits growth and promotes the differentiation of normal keratinocytes by the phosphorylation and activation of the transcription factor STAT-1α but IFN-γ fails to activate STAT-1α in psoriatic keratinocytes. These proliferate out of control, rather like a car going too fast because the accelerator is stuck, which cannot be stopped by putting a foot on the brake. Similarly, subnormal activation of another transcription factor, NFκB, may also be important for the formation of psoriatic plaques, as the absence of NFκB activity in gene knock-out mice has been shown to lead to epidermal hyperproliferation.

Others think that psoriasis is caused by a genetic defect of retinoid signalling and that is why it improves with retinoid treatment. In this context, there are two families of retinoid receptors in the epidermis: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Receptor-specific retinoids are now available that bind to RARs, reduce keratinocyte proliferation, normalize differentiation and reduce infiltration by inflammatory cells.

**Altered epidermal maturation**

During normal keratinization the profile of keratin types in an epidermal cell changes as it moves from the basal layer (K5 and K14) towards the surface (K1 and K10; p. 11). K6 and K16 are produced in psoriasis but their presence is secondary and non-specific, merely a result of increased epidermal proliferation.

**Inflammation**

Psoriasis differs from the ichthyoses (p. 41) in its accumulation of inflammatory cells, and this could be an immunological response to as yet unknown antigens. Certain interleukins and growth factors are elevated, and adhesion molecules are expressed or up-regulated in the lesions. Immune events may well have a primary role in the pathogenesis of the disease of psoriasis and a hypothetical model might run as follows.

1. Keratinocytes are stimulated by various insults (e.g. trauma, infections, drugs, ultraviolet radiation) to release IL-1, IL-8 and IL-18.
2. IL-1 up-regulates the expression of intercellular adhesion molecule-1 (ICAM-1) and E selectin on vascular endothelium in the dermal papillae. CLA positive memory T lymphocytes accumulate in these papillary vessels because their lymphocyte function-associated antigen (LFA-1) sticks to adhesion molecules that are expressed on the vascular endothelium (p. 27).
The dermis must be present for the graft to sustain its psoriasis. The dermal capillary loops in psoriatic plaques are abnormally dilated and tortuous, and these changes come before epidermal hyperplasia in the development of a new plaque. Fibroblasts from psoriatics replicate more rapidly in vitro and produce more glycosaminoglycans than do those from non-psoriatics.

**Precipitating factors**

These include the following.

1. **Trauma**—if the psoriasis is active, lesions can appear in skin damaged by scratches or surgical wounds (the Köbner phenomenon; Fig. 5.1).
2. **Infection**—tonsillitis caused by β-haemolytic streptococci often triggers guttate psoriasis. AIDS often worsens it, or precipitates explosive forms.
3. **Hormonal**—psoriasis frequently improves in pregnancy only to relapse postpartum. Hypocalcaemia secondary to hypoparathyroidism is a rare precipitating cause.
4. **Sunlight**—improves most psoriatics but 10% become worse.
5. **Drugs**—antimalarials, β blockers, IFN-α and lithium may worsen psoriasis. Psoriasis may ‘rebound’ after withdrawal of treatment with systemic steroids or potent topical steroids. The case against non-steroidal anti-inflammatory drugs (NSAIDS) remains unproven.
6. **Cigarette smoking and alcohol**—the effects of confounding variables have been difficult to unravel in most epidemiological studies but there is growing...
Guttate pattern

This is usually seen in children and adolescents and may be the first sign of the disease, often triggered by streptococcal tonsillitis. Numerous small round red macules come up suddenly on the trunk and soon become scaly (Fig. 5.5). The rash often clears in a few months but plaque psoriasis may develop later.

Fig. 5.3 Psoriasis: extensive plaque psoriasis.

Presentation

Common patterns

Plaque pattern

This is the most common type. Lesions are well demarcated and range from a few millimetres to several centimetres in diameter (Fig. 5.3). The lesions are pink or red with large dry silvery-white polygonal scales (like candle grease). The elbows, knees, lower back and scalp are sites of predilection (Fig. 5.4).

Histology (Fig. 5.2)

The main changes are the following.

1. Parakeratosis (nuclei retained in the horny layer).
2. Irregular thickening of the epidermis, but thinning over dermal papillae is apparent clinically when bleeding is caused by scratching and the removal of scales (Auspitz’s sign).
3. Polymorphonuclear leucocyte microabscesses (described originally by Munro).
4. Dilated and tortuous capillary loops in the dermal papillae.
5. T-lymphocyte infiltrate in upper dermis.

Fig. 5.2 Histology of psoriasis (right) compared with normal skin (left).

evidence that both have an independent effect in precipitating or maintaining psoriasis.
7 Emotion—emotional upsets seem to cause some exacerbations.
from the nail bed; Fig. 5.8) and sometimes subungual hyperkeratosi.

Flexures
Psoriasis of the submammary, axillary and anogenital folds is not scaly although the glistening sharply demarcated red plaques (Fig. 5.9), often with fissuring in the depth of the fold, are still readily recognizable. Flexural psoriasis is most common in women and in the elderly, and is more common among HIV-infected individuals than uninfected ones.
Palms and soles

Palmar psoriasis may be hard to recognize as its lesions are often poorly demarcated and barely erythematous. The fingers may develop painful fissures.

Less common patterns

Napkin psoriasis

A psoriasiform spread outside the napkin (nappy/diaper) area may give the first clue to a psoriatic tend-

ency in an infant (Fig. 5.10). Usually it clears quickly but there is an increased risk of ordinary psoriasis developing in later life.

Localized pustular psoriasis (palmo-plantar pustulosis)

This is a recalcitrant, often painful condition which some regard as a separate entity. It affects the palms and soles, which become studded with numerous sterile pustules, 3–10 mm in diameter, lying on an erythematous base. The pustules change to brown macules or scales (Figs 5.11 and 5.12). Generalized pustular psoriasis is a rare but serious condition, with fever and recurrent episodes of pustulation within areas of erythema.

Erythrodermic psoriasis

This is also rare and can be sparked off by the irritant effect of tar or dithranol, by a drug eruption or by the withdrawal of potent topical or systemic steroids. The skin becomes universally and uniformly red with variable scaling (Fig. 5.13). Malaise is accompanied by shivering and the skin feels hot and uncomfortable.
rheumatoid factor are negative and nodules are absent. In patients with spondylitis and sacroiliitis there is a strong correlation with the presence of HLA-B27.

Differential diagnosis

Psoriatic arthropathy
Arthritis occurs in about 5% of psoriatics. Several patterns are recognized. Distal arthritis involves the terminal interphalangeal joints of the toes and fingers, especially those with marked nail changes (Fig. 5.14). Other patterns include involvement of a single large joint; one which mimics rheumatoid arthritis and may become mutilating (Fig. 5.15); and one where the brunt is borne by the sacro-iliac joints and spine. Tests for

Complications

Psoriatic arthropathy
Arthritis occurs in about 5% of psoriatics. Several patterns are recognized. Distal arthritis involves the terminal interphalangeal joints of the toes and fingers, especially those with marked nail changes (Fig. 5.14). Other patterns include involvement of a single large joint; one which mimics rheumatoid arthritis and may become mutilating (Fig. 5.15); and one where the brunt is borne by the sacro-iliac joints and spine. Tests for
This is often confused with nail psoriasis but is more asymmetrical and there may be obvious tinea of neighbouring skin. Uninvolved nails are common. Pitting is not seen and nails tend to be crumbly and discoloured at their free edge.

**Investigations**

1. Biopsy is seldom necessary.
2. Throat swabbing for β-haemolytic streptococci is needed in guttate psoriasis.
3. Skin scrapings and nail clippings may be required to exclude tinea.
4. Radiology and tests for rheumatoid factor are helpful in assessing arthritis.

**Treatment**

The need for this depends both on the patient’s own perception of his or her disability, and on the doctor’s objective assessment of how severe the skin disease is. The two do not always tally.

**General measures**

Explanations and reassurances must be geared to the patient’s or the parent’s intelligence. Information leaflets help to reinforce verbal advice. The doctor as well as the patient should keep the disease in perspective, and treatment must never be allowed to be more troublesome than the disease itself. The disease is not contagious. At present there is no cure for psoriasis; all treatments are suppressive and aimed at either inducing a remission or making the condition more tolerable. However, spontaneous remissions will occur in 50% of patients. Treatment for patients with chronic stable plaque psoriasis is relatively simple and may be safely administered by the family practitioner. However, systemic treatment for severe psoriasis should be monitored by a dermatologist. No treatment, at present, alters the overall course of the disease.

Physical and mental rest help to back up the specific management of acute episodes. Concomitant anxiety and depression should be treated on their own merits (see Table 5.1 for appropriate treatments).
CHAPTER 5

*cholecalciferol* in the skin (p. 12). Calcipotriol and tacalcitol are analogues of cholecalciferol, which do not cause hypercalcaemia and calciuria when used topically in the recommended dose. Both can be used for mild to moderate psoriasis affecting less than 40% of the skin. They work by influencing vitamin D receptors in keratinocytes, reducing epidermal proliferation and restoring a normal horny layer. They also inhibit the synthesis of polyamines (p. 49).

**Calcipotriol (calcipotriene, USA)**

Patients like calcipotriol because it is odourless, colourless and does not stain. It seldom clears plaques of psoriasis completely, but does reduce their scaling and thickness. Local and usually transient irritation may occur with the recommended twice-daily application. One way of lessening this is to combine the use of

### Table 5.1 Treatment options in psoriasis.

<table>
<thead>
<tr>
<th>Type of psoriasis</th>
<th>Treatment of choice</th>
<th>Alternative treatments</th>
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<tbody>
<tr>
<td>Stable plaque</td>
<td>Vitamin D analogue</td>
<td>Coal tar</td>
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<tr>
<td></td>
<td>Local retinoid</td>
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<td></td>
<td>Local steroid</td>
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<td></td>
<td>Dithranol</td>
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<td>Extensive stable plaque (&gt; 30% surface area) recalcitrant to local therapy</td>
<td>UVB</td>
<td>Methotrexate</td>
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<td></td>
<td>PUVA</td>
<td>Cyclosporin A</td>
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<td>PUVA + acitretin</td>
<td>Acitretin</td>
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<td></td>
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<td>Sulfasalazine</td>
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<td>Mycophenolate mofetil</td>
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<tr>
<td>Widespread small plaque</td>
<td>UVB</td>
<td>Vitamin D analogue</td>
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<td></td>
<td></td>
<td>Coal tar</td>
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<tr>
<td>Guttate</td>
<td>Systemic antibiotic</td>
<td>Weak tar preparation</td>
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<td></td>
<td>Emollients while erupting; then UVB</td>
<td>Mild local steroid</td>
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<tr>
<td>Facial</td>
<td>Tacrolimus</td>
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<td></td>
<td>Mild to moderately potent local steroid</td>
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<tr>
<td>Flexural</td>
<td>Tacrolimus</td>
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<tr>
<td></td>
<td>Vitamin D analogue (caution: may irritate)</td>
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<tr>
<td></td>
<td>Mild to moderately potent local steroid + anticanical/fungal</td>
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</tr>
<tr>
<td>Pustular psoriasis of hands and feet</td>
<td>Moderately potent or potent local steroid</td>
<td>Acitretin</td>
</tr>
<tr>
<td></td>
<td>Local retinoid</td>
<td>Topical PUVA</td>
</tr>
<tr>
<td>Acute erythrodermic, unstable or generalized pustular</td>
<td>Inpatient treatment with ichthammol paste</td>
<td>Acitretin</td>
</tr>
<tr>
<td></td>
<td>Local steroid may be used initially with or without wet compresses</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporin A</td>
</tr>
</tbody>
</table>

**Main types of treatment**

These can be divided into four main categories: local, ultraviolet radiation, systemic and combined. Broad recommendations are listed in Table 5.1, but most physicians will have their own favourites. In many ways it is better to become familiar with a few remedies than dabble with many. The management of patients with psoriasis is an art as well as a science and few other skin conditions benefit so much from patience and experience—of both patients and doctors.

**Local treatments**

**Vitamin D analogues**

Ultraviolet radiation helps many patients with psoriasis (see below), perhaps by increasing the production of
calcipotriol with that of a moderately potent steroid, the calcipotriol being applied in the evening and the steroid in the morning (see Topical corticosteroids below). Calcipotriol should not be used on the face. Up to 100 g/week calcipotriol may be used but the manufacturer’s recommendations should be consulted when it is used in children over 6 years old.

Our current practice, which may be unnecessary, is still to check the blood calcium and phosphate levels every 6 months, especially if the psoriasis is widespread or the patient has had calcified renal stones in the past.

**Tacalcitol**

Tacalcitol ointment (not available in the USA) is applied sparingly once daily at bedtime, the maximum amount being 10 g/day. As with calcipotriol, irritation—often transient—may occur. The drug should not be used for longer than a year at a time and is not yet recommended for children.

**Local retinoids**

Tazarotene is a topically active retinoid. It has a selective affinity for RARs and, when bound to these, improves psoriasis by reducing keratinocyte proliferation, normalizing the disturbed differentiation and lessening the infiltrate of dermal inflammatory cells. It is recommended for chronic stable plaque psoriasis on the trunk and limbs covering up to 20% of the body. It is applied sparingly once a day, in the evening, and can be used for courses of up to 12 weeks. It seldom clears psoriasis but reduces the induration, scaling and redness of plaques. It is available as either a 0.05% or 0.1% gel. Like the vitamin D analogues, its main side-effect is irritation. If this occurs, the strength should be reduced to 0.05%; if irritation persists, applications should be cut to alternate days and a combination treatment with a local steroid considered.

In the USA, tazarotene is licensed for children aged 12 years and over; in Europe it is currently licensed only for adults over 18 years old. The drug should not be used in pregnancy or during lactation. Females of childbearing age should use adequate contraception during therapy.

**Topical corticosteroids**

Practice varies from centre to centre and from country to country. Many dermatologists, particularly in the USA, find topical corticosteroids most helpful and use them as the mainstay of their long-term management of stable plaque psoriasis. Patients like them because they are clean and reduce scaling and redness.

In our view such usage is safe, but only under proper supervision by doctors well aware of problems such as dermal atrophy, tachyphylaxis, early relapses, the occasional precipitation of unstable psoriasis (Fig. 5.16) and, rarely, in extensive cases, of adrenal suppression caused by systemic absorption. A commitment by the prescriber to keep the patient under regular clinical review is especially important if more than 50 g/week of a moderately potent topical corticosteroid preparation is being used. Combined tar–steroid preparations may also be helpful (Formulary 1, p. 333).

The regular use of topical corticosteroids is less controversial under the following circumstances.

1 In ‘limited choice’ areas such as the face, ears, genitals and flexures where tar and dithranol are seldom tolerated (mildly potent steroid preparations should be used if possible).

2 For patients who cannot use vitamin D analogues, tar or dithranol because of allergic or irritant reactions (moderately potent preparations, except for ‘no choice’ areas where mildly potent ones should be used if possible).
For unresponsive psoriasis on the scalp, palms and soles (moderately potent, potent and very potent—but only in the short term—preparations).

For patients with minor localized psoriasis (moderately potent or potent preparations).

A combination ointment of calcipotriol and betamethasone dipropionate (a potent corticosteroid) has recently been marketed in the UK. The maximum dose should not exceed 15g/day or 100g/week and the ointment should not be applied for longer than 4 weeks.

**Dithranol (anthralin)**

Dithranol is rarely used in the USA nowadays but remains popular in the UK. Like coal tar it inhibits DNA synthesis, but some of its benefits may be brought about by the formation of free radicals of oxygen.

Dithranol is more tricky to use than coal tar. It has to be applied carefully, to the plaques only; and, if left on for more than 30 min, must be covered with gauze dressings. It is irritant, so treatment should start with a weak (0.1%) preparation, thereafter the strength can be stepped up at weekly intervals. Dithranol stronger than 1% is seldom necessary. Irritation of the surrounding skin can be lessened by the application of a protective bland paste, e.g. zinc paste.

Dithranol stains normal skin, but the purple-brown discoloration peels off after a few days. It also stains bathtubs, clothes—and anything else it touches. One popular regimen is to apply dithranol daily for 5 days in the week; after 1 month many patients will be clear.

Short contact therapy, in which dithranol is applied for no longer than 30 min, is also effective. Initially a test patch of psoriasis is treated with a 0.1% dithranol cream, left on for 20 min and then washed off. If there is no undue reaction, the application can be extended the next day and, if tolerated, can be left on for 30 min. After the cream is washed off, a bland application such as soft white paraffin or emulsifying ointment is applied. Depending on response, the strength of the dithranol can be increased from 0.1 to 2% over 2–3 weeks. Suitable preparations are listed in Formulary 1 (p. 337).

Dithranol is too irritant to apply to the face, the inner thighs, genital region or skin folds. Special care must be taken to avoid contact with the eyes. Recent research has shown that applying triethanolamine after the dithranol has been removed reduces inflammation and staining without diminishing the therapeutic effect.

**Coal tar preparations**

Crude coal tar and its distillation products have been used to treat psoriasis for many years. Their precise mode of action is uncertain but tar does inhibit DNA synthesis.

Many preparations are available but it is wise to become familiar with a few. The less refined tars are smelly, messy and stain clothes, but are more effective than the cleaner refined preparations. Tar emulsions can also be added to the bath. Suitable preparations are listed in Formulary 1 (p. 337). Surprisingly, no increase in skin cancer has been found in patients treated for long periods with tar preparations; it has even been suggested that psoriatics are less likely than normal to develop skin cancer.

**Ultraviolet radiation**

Most patients improve with natural sunlight and should be encouraged to sunbathe. During the winter, courses of artificial ultraviolet radiation (UVB), as an outpatient or at home, may help (Fig. 5.17). Both broadband UVB and narrow band UVB (311 nm) can be used. Treatments should be given by an expert, twice to three times weekly for 8 weeks. Goggles should be worn. The initial dose is calculated either by establishing the skin type (p. 233) or by determining...
Photochemotherapy (PUVA)

In this ingenious therapy, a drug is photo-activated in the skin by ultraviolet radiation. An oral dose of 8-methoxypsoralen (8-MOP) or 5-methoxypsoralen (5-MOP) is followed by exposure to long-wave ultraviolet radiation (UVA: 320–400 nm). The psoralen reaches the skin and, in the presence of UVA, forms photo-adducts with DNA pyrimidine bases and cross-links between complementary DNA strands; this inhibits DNA synthesis and epidermal cell division.

The 8-MOP (crystalline formulation 0.6–0.8 mg/kg body weight or liquid formulation 0.3–0.4 mg/kg) or 5-MOP (1.2–1.6 mg/kg) is taken 1–2 h before exposure to a bank of UVA tubes mounted in a cabinet similar to that seen in Fig. 5.17. Psoralens may also be administered in bath water for those unable to tolerate the oral regimen. The initial exposure is calculated either by determining the patient’s minimal phototoxic dose (the least dose of UVA that after ingestion of 8-MOP produces a barely perceptible erythema 72 h after testing) or by assessing skin colour and ability to tan. The usual starting dose is from 0.5 J/cm² (skin type I: always burns and never tans) to 2.0 J/cm² (skin type IV: never burns and always tans). Treatment is given two or three times a week with increasing doses of UVA, depending on erythema production and the therapeutic response. Protective goggles are worn during radiation and UVA opaque plastic glasses must be used after taking the tablets and for 24 h after each treatment (see below). All phototherapy equipment should be serviced and calibrated regularly by trained personnel. An accurate record of each patient’s cumulative dosage and number of treatments should be kept.

Clearance takes 5–10 weeks. Thereafter it is often possible to keep the skin clear by PUVA once a fortnight or every 3 weeks. However, as the side-effects of PUVA relate to its cumulative dose (see below), maintenance therapy should not be used unless alternative treatments prove to be unsatisfactory. As far as possible, PUVA therapy is avoided in younger patients.

Side effects

Painful erythema is the most common side-effect but the risk of this can be minimized by careful dosimetry. One-quarter of patients itch during and immediately after radiation; fewer feel nauseated after taking 8-MOP. 5-MOP, not yet available in the USA, is worth trying if these effects become intolerable. Long-term side-effects include premature ageing of the skin (with mottled pigmentation, scattered lentigines, and dysplasia).
wrinkles and atrophy), cutaneous malignancies (usually after a cumulative dose greater than 1000 J or after more than 250 treatments) and, theoretically at least, cataract formation. The use of UVA blocking glasses (see above) for 24 h after each treatment should protect against the latter. The long-term side-effects relate to the total amount of UVA received over the years; this must be recorded and kept as low as possible, without denying treatment when it is clearly needed.

Retinoids

Acitretin (10–25 mg daily; Formulary 2, p. 349) is an analogue of vitamin A, and is one of the few drugs helpful in pustular psoriasis. It is also used to thin down thick hyperkeratotic plaques. Minor side-effects are frequent and dose-related. They include dry lips, mouth, vagina and eyes, peeling of the skin, pruritus, thinning of the hair, and unpleasant paronychia. All settle on stopping or reducing the dosage of the drug, but the use of emollients and artificial tears is often recommended.

Acitretin can be used on its own for long periods, but regular blood tests are needed to exclude abnormal liver function and the elevation of serum lipids (mainly triglycerides but also cholesterol). Yearly X-rays should detect bone spurs and ossification of ligaments, especially the paraspinal ones (disseminated interstitial skeletal hyperostosis (DISH) syndrome). Children, and those with persistently abnormal liver function tests or hyperlipidaemia, should not be treated.

The most important side-effect is teratogenicity and acitretin should not normally be prescribed to women of childbearing age. If, for unavoidable clinical reasons, it is still the drug of choice, effective oral contraceptive measures must be taken and, in view of the long half-life of its metabolite, these should continue for 2 years after treatment has ceased. Blood donation should be avoided for a similar period.

Retinoids and PUVA act synergistically and are often used together in the so-called Re-PUVA regimen. This clears plaque psoriasis quicker than PUVA alone, and needs a smaller cumulative dose of UVA. The standard precautions for both PUVA and retinoid treatment should, of course, still be observed.

Methotrexate

This folic acid antagonist (Formulary 2, p. 348) inhibits DNA synthesis during the S phase of mitosis. After an initial trial dose of 2.5 mg, in an adult of average weight, the drug is given orally once a week and the dose increased gradually to a maintenance one of 7.5–15 mg/week. This often controls even aggressive psoriasis. The drug is eliminated largely by the kidneys and so the dose must be reduced if renal function is poor. Aspirin and sulphonamides displace the drug from binding with plasma albumin, and frusemide (furosemide) decreases its renal clearance: note must therefore be taken of concurrent drug therapy (Formulary 2, p. 348) and the dose reduced accordingly. Minor and temporary side-effects, such as nausea and malaise, are common in the 48 h after administration. The most serious drawback to this treatment is hepatic fibrosis, the risk of which is greatly increased in those who drink an excessive amount of alcohol. Unfortunately, routine liver function tests and scans cannot predict this reliably, and a liver biopsy to exclude active liver disease is advised for those with risk factors. Exceptions are made for patients over 70 years old and when only short-term treatment with methotrexate is anticipated. Liver biopsy before treatment, or early in the course of therapy, should be repeated after every cumulative dose of 1.5–2 g, especially in less than perfectly healthy drinking adults. Blood checks to exclude marrow suppression, and to monitor renal and liver function, should also be performed—weekly at the start of treatment, with the interval being slowly increased to monthly or every other month depending on when stable maintenance therapy is established.

The drug is teratogenic and should not be given to females in their reproductive years. Oligospermia has been noted in men and fertility may be lowered; however, a child fathered by a man on methotrexate can be expected to be normal. Folic acid, 5 mg daily, taken on days when the patient does not have methotrexate, can lessen nausea and reduce marrow suppression. Methotrexate should not be taken at the same time as systemic steroids or cyclosporin.

Cyclosporin

Cyclosporin inhibits cell-mediated immune reactions. It blocks resting lymphocytes in the G0 or early G1 phase of the cell cycle and inhibits lymphokine release, especially that of IL-2.

Cyclosporin is effective in severe psoriasis, but patients needing it should be under the care of specialists. The initial daily dose is 3–4 mg/kg/day and not more
PSORIASIS

May develop gingival hyperplasia. Treatment with cyclosporin should not continue for longer than 1 year without careful assessment and close monitoring.

Other systemic drugs

Antimetabolites such as mycophenolate mofetil, 6-mercaptopurine, azathioprine and hydroxyurea help psoriasis, but less than methotrexate; they tend to damage the marrow rather than the liver. Regular blood monitoring is again essential. Sulfasalazine occasionally helps psoriasis.

Combination therapy

If psoriasis is resistant to one treatment, a combination of treatments used together may be the answer. Combination treatments can even prevent side-effects by allowing less of each drug to be used. Common combinations include topical vitamin D analogues with either local steroids or UVB, dithranol following a tar bath and UVB (Ingram regimen) and coal tar following a tar bath and UVB (Goeckerman regimen).

Rotational therapy may also minimize the toxicity of some treatments—an example would be PUVA, methotrexate, acitretin and cyclosporin, each used separately for 1–2 years before moving on to the next treatment.

Future treatments

The development of retinoids and vitamin D analogues over the last decade has heralded a resurgence of interest in new treatments for psoriasis. The idea of...

Fig. 5.18 Therapeutic targets to reduce T-helper cell proliferation in psoriasis. Proprietary names of experimental drugs given beside arrows.

than 5 mg/kg/day. With improvement the dose can often be reduced but the side-effects of long-term treatment include hypertension, kidney damage and persistent viral warts with a risk of skin cancer. Blood pressure and renal function should be assessed carefully before starting treatment. The serum creatinine should be measured two or three times before starting therapy to be sure of the baseline and then every other week for the first 3 months of therapy. Thereafter, if the results are stable, the frequency of testing will depend on the dosage (monthly for > 2.5 mg/kg/day or every other month for < 2.5 mg/kg/day). The dosage should be reduced if the serum creatinine concentration rises to 30% above the baseline level on two occasions within 2 weeks. If these changes do not reverse themselves when the dosage has been reduced for 1 month, then the drug should be stopped.

Hypertension is a common side-effect of cyclosporin: nearly 50% of patients develop a systolic blood pressure over 160 mmHg and/or a diastolic blood pressure over 95 mmHg. Usually these rises are mild or moderate, and respond to concomitant treatment with a calcium channel blocker, such as nifedipine. If this cannot be tolerated, an angiotensin-converting enzyme inhibitor should be used under specialist supervision. Diuretics, which may themselves worsen renal function, and β blockers, which may themselves worsen psoriasis, should probably be avoided. Cyclosporin interacts with a number of drugs (Formulary 2, p. 347) and these should be avoided.

It is also advisable to watch levels of cholesterol, triglycerides, potassium and magnesium, and advise patients that they will become hirsute and that they...
ents are already participating in trials of humanized monoclonal antibodies. Even vaccination with pathogenic T cells or T-cell receptor peptides is no longer science fiction.

Further reading


LEARNING POINTS

1. Discuss a treatment plan with the patient. Consider disability, cost, time, mess and risk of systemic therapy to general health.
2. The treatment must not be worse than the disease.
3. Do not aggravate eruptive psoriasis.
4. Never use systemic steroids.
5. Avoid the long-term use of potent or very potent topical corticosteroids.
6. Never promise a permanent cure, but be encouraging.
7. Great advances have been made over the last 20 years in the treatment of severe psoriasis, but patients taking modern systemic agents require careful monitoring.

of using a weekly injection to control psoriasis is no longer a pipe-dream. The immunologically based pathogenesis of psoriasis presents many targets for therapeutic exploitation; most involve inhibiting the proliferation of T-helper lymphocytes (Fig. 5.18), others block key cytokines such as TNF-α (e.g. with infliximab or etanercept), or inhibit the adhesion of inflammatory cells to the endothelium of dermal vessels (e.g. with antibodies against E selectin). Patients are already participating in trials of humanized monoclonal antibodies. Even vaccination with pathogenic T cells or T-cell receptor peptides is no longer science fiction.
Psoriasis is not the only skin disease that is sharply marginated and scaly. Table 6.1 lists some of the most common ones. Eczema can also be raised and scaly, but is usually poorly marginated and fissures, crusts or lichenifies (Chapter 7). Psoriasis is discussed in Chapter 5.

**Pityriasis rosea**

**Cause**

The cause of pityriasis rosea is not known. An infectious agent has always seemed likely but has not yet been proven: human herpesvirus 7 is the latest suspect. The disorder seems not to be contagious.

**Presentation**

Pityriasis rosea is common, particularly during the winter. It mainly affects children and young adults, and second attacks are rare. Most patients develop one plaque (the ‘herald’ or ‘mother’ plaque) before the others (Fig. 6.1). It is larger (2–5 cm in diameter) than later lesions, and is rounder, redder and more scaly. After several days many smaller plaques appear, mainly on the trunk, but some also on the neck and extremities. About half of the patients complain of itching. An individual plaque is oval, salmon pink and shows a delicate scaling, adherent peripherally as a collarette. The configuration of such plaques is often characteristic. Their longitudinal axes run down and out from the spine (Fig. 6.2), along the lines of the ribs. Purpuric lesions are rare.

![Fig. 6.1](image.png) The herald plaque of pityriasis rosea is usually on the trunk and is larger than the other lesions. Its annular configuration is shown well here.

**Table 6.1** Some important papulosquamous diseases.

<table>
<thead>
<tr>
<th>Disease</th>
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<tbody>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Pityriasis rosea</td>
</tr>
<tr>
<td>Lichen planus</td>
</tr>
<tr>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td>Parapsoriasis</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Pityriasis lichenoides</td>
</tr>
<tr>
<td>Discoid lupus erythematosus</td>
</tr>
<tr>
<td>Tinea</td>
</tr>
<tr>
<td>Nummular eczema</td>
</tr>
<tr>
<td>Seborrhoic dermatitis</td>
</tr>
<tr>
<td>Secondary syphilis</td>
</tr>
<tr>
<td>Drug eruptions</td>
</tr>
</tbody>
</table>

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63 Other papulosquamous disorders
Investigations

Because secondary syphilis can mimic pityriasis rosea so closely, testing for syphilis is usually wise.

Treatment

No treatment is curative, and active treatment is seldom needed. A moderately potent topical steroid or calamine lotion will help the itching. One per cent salicylic acid in soft white paraffin or emulsifying ointment reduces scaling. Sunlight or artificial UVB often relieves pruritus and may hasten resolution.

Lichen planus

Cause

The precise cause of lichen planus is unknown, but the disease seems to be mediated immunologically. Lymphocytes abut the epidermal basal cells and damage them. Chronic graft-vs.-host disease can cause an eruption rather like lichen planus in which histoincompatibility causes lymphocytes to attack the epidermis. Lichen planus is also associated with autoimmune disorders, such as alopecia areata, vitiligo and ulcerative colitis, more commonly than would be expected by chance. Drugs too can cause lichen planus (see below). Some patients with lichen planus also have a hepatitis B or C infection—but lichen planus itself is not infectious.

Presentation

Typical lesions are violaceous or lilac-coloured, intensely itchy, flat-topped papules that usually arise on the extremities, particularly on the volar aspects.
of the wrists and legs (Fig. 6.3). A close look is needed to see a white streaky pattern on the surface of these papules (Wickham’s striae). White asymptomatic lacy lines, dots, and occasionally small white plaques, are also found in the mouth, particularly inside the cheeks, in about 50% of patients (Fig. 6.4), and oral lesions may be the sole manifestation of the disease. The genital skin may be similarly affected (see Fig. 13.37). Variants of the classical pattern are rare and often difficult to diagnose (Table 6.2). Curiously, although the skin plaques are usually itchy, patients rub rather than scratch, so that excoriations are uncommon. As in psoriasis, the Köbner phenomenon may occur (Fig. 6.5). The nails are usually normal, but in about 10% of patients show changes ranging from

**Table 6.2** Variants of lichen planus.

<table>
<thead>
<tr>
<th>Variant</th>
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<tbody>
<tr>
<td>Annular</td>
</tr>
<tr>
<td>Atrophic</td>
</tr>
<tr>
<td>Bullous</td>
</tr>
<tr>
<td>Follicular</td>
</tr>
<tr>
<td>Hypertrophic  (Fig. 6.5)</td>
</tr>
<tr>
<td>Ulcerative</td>
</tr>
</tbody>
</table>

Fig. 6.3 Shiny flat-topped papules of lichen planus. Note the Wickham’s striae.

Fig. 6.4 Lichen planus: classic white lacy network lying on the buccal mucosa.

Fig. 6.5 Lichen planus: striking Köbner effect on the forearm.

Fig. 6.6 The thickened purplish lesions characteristic of hypertrophic lichen planus on the shins.
fine longitudinal grooves to destruction of the entire nail fold and bed (see Fig. 13.26). Scalp lesions can cause a patchy scarring alopecia.

Course

Individual lesions may last for many months and the eruption as a whole tends to last about 1 year. However, the hypertrophic variant of the disease, with thick warty lesions usually around the ankles (Fig. 6.6), often lasts for many years. As lesions resolve, they become darker, flatter and leave discrete brown or grey macules. About one in six patients will have a recurrence.

Complications

Nail and hair loss can be permanent. The ulcerative form of lichen planus in the mouth may lead to squamous cell carcinoma. Ulceration, usually over bony prominences, may be disabling, especially if it is on the soles. Any association with liver disease is probably caused by the coexisting hepatitis infections mentioned above.

Differential diagnosis

Lichen planus should be differentiated from the other papulosquamous diseases listed in Table 6.1. Lichenoid drug reactions can mimic lichen planus closely. Gold and other heavy metals have often been implicated. Other drug causes include antimalarials, β blockers, non-steroidal anti-inflammatory drugs, para-aminobenzoic acid, thiazide diuretics and penicillamine. Contact with chemicals used to develop colour film can also produce similar lesions. It may be hard to tell lichen planus from generalized discoid lupus erythematosus if only a few large lesions are present, or if the eruption is on the palms, soles or scalp. Wickham’s striae or oral lesions favour the diagnosis of lichen planus. Oral candidiasis (p. 000) can also cause confusion.

Investigations

The diagnosis is usually obvious clinically. The histology is characteristic (Fig. 6.7), so a biopsy will confirm the diagnosis if necessary.

Treatment

Treatment can be difficult. If drugs are suspected as the cause, they should be stopped and unrelated ones substituted. Potent topical steroids will sometimes relieve symptoms and flatten the plaques. Systemic steroid courses work too, but are recommended only in special situations (e.g. unusually extensive involvement, nail destruction or painful and erosive oral lichen planus). Treatment with photochemotherapy with psoralen and ultraviolet A (PUVA; p. 59) or with narrow-band UVB (p. 58) may reduce pruritus and help to clear up the skin lesions. Acitretin (Formulary 2, p. 349) has also helped some patients with stubborn lichen planus. Antihistamines may blunt the itch. Mucous membrane lesions are usually asymptomatic and do not require treatment; if they do, then applications of a corticosteroid or tacrolimus in a gel base may be helpful.

![Fig. 6.7 Histology of lichen planus.](image)
Differential diagnosis

Psoriasis is the disorder closest in appearance to pityriasis rubra pilaris, but lacks its slightly orange tinge. The thickening of the palms and soles, the follicular erythema in islands of uninvolved skin, and follicular plugging within the plaques, especially over the knuckles, are other features that help to separate them.

Investigations

A biopsy may help to distinguish psoriasis from pityriasis rubra pilaris; but, even so, the two disorders share many histological features.

Treatment

The disorder responds slowly to systemic retinoids such as acitretin (in adults, 25–50 mg/day for 6–8 months; p. 349). Oral methotrexate in low doses, once a week may also help (p. 348). Topical steroids and keratolytics (e.g. 2% salicylic acid in soft white paraffin) reduce inflammation and scaling, but usually do not suppress the disorder completely. Systemic steroids are not indicated.

Parapsoriasis and premycotic eruption

Parapsoriasis is a contentious term, which many would like to drop. We still find it useful clinically for lesions that look a little like psoriasis but which scale subtly.
rather than grossly, and which persist despite anti-psoriasis treatment. It is worth trying to distinguish a benign type of parapsoriasis from a premycotic type, which is a forerunner of mycosis fungoides, a cutaneous T-cell lymphoma (Fig. 6.9)—although they can look alike early in their development. However, even the term ‘premycotic’ is disputed, as some think that these lesions are mycosis fungoides right from the start, preferring the term ‘patch stage cutaneous T-cell lymphoma’ (p. 280).

Cause
The cause is otherwise unknown.

Presentation
Pink scaly well-marginated plaques appear, typically on the buttocks, breasts, abdomen or flexural skin. The distinguishing features of the small-plaque (benign) and large-plaque (premycotic/prelymphomatous) types are given in Table 6.3. Perhaps the most important point to look for is the presence of poikiloderma (atrophy, telangiectasia and reticulate pigmentation) in the latter type. Both conditions are stubborn in their response to topical treatment, although often responding temporarily to PUVA. Itching is variable.

Complications
Patients with suspected premycotic/prelymphomatous eruptions should be followed up carefully, even though the development of cutaneous T-cell lymphoma may not occur for years. If poikiloderma or induration develops, the diagnosis of a cutaneous T-cell lymphoma becomes likely.

Differential diagnosis
This includes psoriasis, tinea and nummular (discoid) eczema. In contrast to psoriasis and pityriasis rosea, the lesions of parapsoriasis, characteristically, are asymmetrical. Topical steroids can cause atrophy and confusion.

Investigations
Several biopsies should be taken if a premycotic eruption is suspected, if possible from thick or atrophic untreated areas. These may suggest an early cutaneous T-cell lymphoma, with bizarre mononuclear cells both in the dermis and in microscopic abscesses within the epidermis. Electron microscopy may show abnormal lymphocytes with convoluted nuclei in the dermis or epidermis, although the finding of these cells, especially in the dermis, is non-specific. DNA probes can determine monoclonality of the T cells within the lymphoid infiltrate of mycosis fungoides based on rearrangements of the T-cell receptor genes (p. 19). The use of these probes and of immunophenotyping

<table>
<thead>
<tr>
<th>Parapsoriasis (benign type)</th>
<th>Premycotic/prelymphomatous eruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller plaques</td>
<td>Larger</td>
</tr>
<tr>
<td>Yellowish</td>
<td>Not yellow—pink, or slightly violet, or brown</td>
</tr>
<tr>
<td>Sometimes finger-shaped lesions</td>
<td>Asymmetrical with bizarre outline</td>
</tr>
<tr>
<td>running around the trunk</td>
<td></td>
</tr>
<tr>
<td>No atrophy</td>
<td>Atrophy ± poikiloderma</td>
</tr>
<tr>
<td>Responds to UVB</td>
<td>Responds better to PUVA</td>
</tr>
<tr>
<td>Remains benign although rarely clears</td>
<td>May progress to a cutaneous T-cell lymphoma</td>
</tr>
</tbody>
</table>

Table 6.3 Distinguishing features of parapsoriasis and premycotic/prelymphomatous eruptions.
helps to differentiate benign parapsoriasis from premycotic/prelymphomatous eruptions.

**Treatment**

Treatment is controversial. Less aggressive treatments are used for the benign type of parapsoriasis. Usually, moderately potent steroids or ultraviolet radiation bring some resolution, but lesions tend to recur when these are stopped. For premycotic/prelymphomatous eruptions, treatment with PUVA (p. 59) or with topical nitrogen mustard paints, is advocated by some, although it is not clear that this slows down or prevents the development of a subsequent cutaneous T-cell lymphoma.

**Pityriasis lichenoides**

Pityriasis lichenoides is uncommon. It occurs in two forms. The numerous small circular scaly macules and papules of the chronic type are easy to confuse with guttate psoriasis (p. 51). However, their scaling is distinctive in that single silver-grey scales surmount the lesions (mica scales). The acute type is characterized by papules that become necrotic and leave scars like those of chickenpox. More often than not there are a few lesions of the chronic type in the acute variant and vice versa. UVB radiation can reduce the number of lesions and spontaneous resolution occurs eventually.

**Other papulosquamous diseases**

Discoid lupus erythematosus is typically papulosquamous; it is discussed with subacute cutaneous lupus erythematosus in Chapter 10. Fungus infections are nummular and scaly and can appear papulosquamous or eczematous; they are dealt with in Chapter 14. Seborrhoeic and nummular discoid eczema are discussed in Chapter 7. Secondary syphilis is discussed in Chapter 14.

**Erythroderma/exfoliative dermatitis**

Sometimes the whole skin becomes red and scaly (see Fig. 5.13). The disorders that can cause this are listed in Table 6.4. The best clue to the underlying cause is a history of a previous skin disease. Sometimes the histology is helpful but often it is non-specific. ‘Erythroderma’ is the term used when the skin is red with little or no scaling, while the term ‘exfoliative dermatitis’ is preferred if scaling predominates.

Most patients have lymphadenopathy, and many have hepatomegaly as well. If the condition becomes chronic, tightness of the facial skin leads to ectropion, scalp and body hair may be lost, and the nails become thickened and may be shed too. Temperature regulation is impaired and heat loss through the skin usually makes the patient feel cold and shiver. Oedema, high output cardiac failure, tachycardia, anaemia, failure to sweat and dehydration can occur. Treatment is that of the underlying condition.

**Further reading**


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**Table 6.4** Some causes of erythroderma/exfoliative dermatitis.

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Pityriasis rubra pilaris</td>
</tr>
<tr>
<td>Ichthyosiform erythroderma</td>
</tr>
<tr>
<td>Pemphigus erythematosus</td>
</tr>
<tr>
<td>Contact, atopic, or seborrhoeic eczema</td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
</tr>
<tr>
<td>Lymphoma (including the Sézary syndrome)</td>
</tr>
<tr>
<td>Drug eruptions</td>
</tr>
<tr>
<td>Crusted (Norwegian) scabies</td>
</tr>
</tbody>
</table>

---

**LEARNING POINTS**

The dangers of erythroderma are the following.

1. Poor temperature regulation.
2. High-output cardiac failure.
3. Protein deficiency.
The disorders grouped under this heading are the most common skin conditions seen by family doctors, and make up some 20% of all new patients referred to our clinics.

**Terminology**

The word ‘eczema’ comes from the Greek for ‘boiling’—a reference to the tiny vesicles (bubbles) that are often seen in the early acute stages of the disorder, but less often in its later chronic stages. ‘Dermatitis’ means inflammation of the skin and is therefore, strictly speaking, a broader term than eczema—which is just one of several possible types of skin inflammation.

In the past too much time has been devoted to trying to distinguish between these two terms. To us, they mean the same thing. This approach is now used by most dermatologists, although many stick to the term eczema when talking to patients for whom ‘dermatitis’ may carry industrial and compensation overtones, which can stir up unnecessary legal battles. In this book contact eczema is the same as contact dermatitis; seborrhoeic eczema the same as seborrhoeic dermatitis, etc.

**Classification of eczema**

This is a messy legacy from a time when little was known about the subject. As a result, some terms are based on the appearance of lesions, e.g. discoid eczema and hyperkeratotic eczema, while others reflect outmoded or unproven theories of causation, e.g. infective eczema and seborrhoeic eczema. Classification by site, e.g. flexural eczema and hand eczema, is equally unhelpful.

Eczema is a reaction pattern. Many different stimuli can make the skin react in the same way, and several of these may be in action at the same time (Fig. 7.1). This can make it hard to be sure which type of eczema is present; and even experienced dermatologists admit that they can only classify some two-thirds of the cases they see. To complicate matters further, the physical signs that make up eczema, although limited, can be jumbled together in an infinite number of ways, so that no two cases look alike.

![Fig. 7.1 The causes of eczema.](image)
help to produce spongiosis (p. 22); and that their secretion by keratinocytes can be elicited by T lymphocytes, irritants, bacterial products and other stimuli (see Fig. 2.11).

**Histology** (Fig. 7.2)

The clinical appearance of the different stages of eczema mirrors their histology. In the acute stage, oedema in the epidermis (spongiosis) progresses to the formation of intraepidermal vesicles, which may coalesce into larger blisters or rupture. The chronic stages of eczema show less spongiosis and vesication but more thickening of the prickle cell layer (acanthosis) and horny layers (hyperkeratosis and parakeratosis).
These changes are accompanied by a variable degree of vasodilatation and infiltration with lymphocytes.

**Clinical appearance**

The different types of eczema have their own distinguishing marks, and these will be dealt with later; most share certain general features, which it is convenient to consider here. The absence of a sharp margin is a particularly important feature that separates eczema from most papulosquamous eruptions.

**Acute eczema**

Acute eczema (Figs 7.3 and 7.4) is recognized by its:
- weeping and crusting;
- blistering—usually with vesicles but, in fierce cases, with large blisters;
- redness, papules and swelling—usually with an ill-defined border; and
- scaling.

**Chronic eczema**

Chronic eczema may show all of the above changes but in general is:
- less vesicular and exudative;
- more scaly, pigmented and thickened;
- more likely to show lichenification (Fig. 7.5)—a dry leathery thickened state, with increased skin markings, secondary to repeated scratching or rubbing; and
- more likely to fissure.

![Fig. 7.3 Acute vesicular contact eczema of the hand.](image)

![Fig. 7.4 Vesicular and crusted contact eczema of the face (cosmetic allergy).](image)

![Fig. 7.5 Lichenification of the wrists—note also the increased skin markings on the palms (‘atopic palms’).](image)

**LEARNING POINTS**

1. Eczema is like jazz; it is hard to define—but it should be easy to recognize if you bear in mind the physical signs listed above.
2. If it does not itch, it is probably not eczema.
Complications

Heavy bacterial colonization is common in all types of eczema but overt infection is most troublesome in the seborrhoeic, nummular and atopic types. Local superimposed allergic reactions to medicaments can provoke dissemination, especially in gravitational eczema.

All severe forms of eczema have a huge effect on the quality of life. An itchy sleepless child can wreck family life. Eczema can interfere with work, sporting activities and sex lives. Jobs can be lost through it.

Differential diagnosis

This falls into two halves. First, eczema has to be separated from other skin conditions that look like it. Table 7.2 plots a way through this maze. Always consider the possibility of discoid eczema, not the various pityriases (rosea, versicolor, and rubra pilaris) and drug eruptions (Chapter 22).

### Table 7.2 Is the rash eczematous?

<table>
<thead>
<tr>
<th>Atypical physical signs?</th>
<th>Consider other erythematous-squamous eruptions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sharply marginated, strong colour, very scaly? Points of elbows and knees involved?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Itchy social contacts? Face spared? Burrows found? Genitals and nipples affected?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mouth lesions? Violaceous tinge? Shiny flat topped papules?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Annular lesions with active scaly edges?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Localized to palms and soles? Obvious pustules?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Unusually swollen; on the face?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

| Consider dermatitis herpetiformis, not the various pityriases (rosea, versicolor, and rubra pilaris) and drug eruptions (Chapter 22) |
remember that eczemas are scaly, with poorly defined margins.

Occasionally a biopsy is helpful in confirming a diagnosis of eczema, but it will not determine the cause or type. Once the diagnosis of eczema becomes solid, look for clinical pointers towards an external cause. This determines both the need for investigations and the best line of treatment. Sometimes an eruption will follow one of the well-known patterns of eczema, such as the way atopic eczema picks out the skin behind the knees, and a diagnosis can then be made readily enough. Often, however, this is not the case, and the history then becomes especially important.

A contact element is likely if:
• there is obvious contact with known irritants or allergens;
• the eruption clears when the patient goes on holiday, or at the weekends;
• the eczema is asymmetrical, or has a linear or rectilinear configuration; or
• the rash picks out the eyelids, external ear canals, hands and feet, the skin around stasis ulcers, or the peri-anal skin.

Investigations

Each pattern of eczema needs a different line of inquiry.

Exogenous eczema

Here the main decision is whether or not to undertake patch testing (p. 35) to confirm allergic contact dermatitis and to identify the allergens responsible for it. In patch testing, standardized non-irritating concentrations of common allergens are applied to the normal skin of the back. If the patient is allergic to the allergen, eczema will develop at the site of contact after 48–96 h. Patch testing with irritants is of no value in any type of eczema, but testing with suitably diluted allergens is essential in suspected allergic contact eczema. The technique is not easy. Its problems include separating irritant from allergic patch test reactions, and picking the right allergens to test. If legal issues depend on the results, testing should be carried out by a dermatologist who will have the standard equipment and a suitable selection of properly standardized allergens (see Fig. 3.7). Patch testing can be used to confirm a suspected allergy or, by the use of a battery of common sensitizers, to discover unsuspected allergies, which then have to be assessed in the light of the history and the clinical picture. A visit to the home or workplace may help with this.

Photopatch testing is more specialized and facilities are only available in a few centres. A chemical is applied to the skin for 24 h and then the site is irradiated with a suberythema dose of ultraviolet irradiation; the patches are inspected for an eczematous reaction 48 h later.

Other types of eczema

The only indication for patch testing here is when an added contact allergic element is suspected. This is most common in gravitational eczema; neomycin, framycetin, lanolin or preservative allergy can perpetuate the condition and even trigger dissemination. Ironically rubber gloves, so often used to protect eczematous hands, can themselves sensitize.

The role of prick testing in atopic eczema is discussed on p. 36.

Patients with atopic dermatitis often have multiple type I reactions to foods, danders, pollens, dusts and moulds. Some find the measurement of serum total immunoglobulin E (IgE), and of IgE antibodies specific to certain antigens, not only useful in diagnosing the atopic state, but also helpful when advising on the role of dietary and environmental allergens in causing or perpetuating atopic dermatitis, particularly in children. Total and specific IgE antibodies are measured by a radioallergosorbent test (RAST). Prick and RAST testing give similar results but many now prefer the more expensive RAST test as it carries no risk of anaphylaxis, is easier to perform and is less time consuming.

If the eczema is worsening despite treatment, or if there is much crusting, heavy bacterial colonization may be present. Opinions vary about the value of cultures for bacteria and candida, but antibiotic treatment may be helpful. Scrapings for microscopical examination (p. 35) and culture for fungus will rule out tinea if there is clinical doubt—as in some cases of discoid eczema.

Finally, malabsorption should be considered in otherwise unexplained widespread pigmented atypical patterns of endogenous eczema.
Treatment

Acute weeping eczema

This does best with rest and liquid applications. Non-steroidal preparations are helpful and the techniques used will vary with the facilities available and the site of the lesions. In general practice a simple and convenient way of dealing with weeping eczema of the hands or feet is to use thrice daily 10-min soaks in a cool 0.65% aluminium acetate solution (Formulary 1, p. 329)—saline or even tap water will do almost as well—each soaking being followed by a smear of a corticosteroid cream or lotion and the application of a non-stick dressing or cotton gloves. One reason for dropping the dilute potassium permanganate solution that was once so popular is because it stains the skin and nails brown.

Wider areas on the trunk respond well to corticosteroid creams and lotions. However, traditional remedies such as exposure and frequent applications of calamine lotion, and the use of half-strength magenta paint for the flexures are also effective.

An experienced doctor or nurse can teach patients how to use wet dressings, and supervise this. The aluminium acetate solution, saline or water, can be applied on cotton gauze, under a polythene covering, and changed twice daily. Details of wet wrap techniques are given below. Rest at home will help too.

Wet wrap dressings

This is a labour-intensive, but highly effective technique, of value in the treatment of troublesome atopic eczema in children. After a bath, a corticosteroid is applied to the skin and then covered with two layers of tubular dressing—the inner layer already soaked in warm water, the outer layer being applied dry. Cotton pyjamas or a T-shirt can be used to cover these, and the dressings can then be left in place for several hours. The corticosteroid may be one that is rapidly metabolized after systemic absorption such as a beclomethasone (beclometasone) dipropionate ointment diluted to 0.025% (available only in the UK). Alternatives include 1 or 2.5% hydrocortisone cream for children and 0.025 or 0.1% triamcinolone cream for adults. The bandages can be washed and reused. The evaporation of fluid from the bandages cools the skin and provides rapid relief of itching. With improvement, the frequency of the dressings can be cut down and a moisturiser can be substituted for the corticosteroid. Parents can be taught the technique by a trained nurse, who must follow up treatment closely. Parents easily learn how to modify the technique to suit the needs of their own child. Side-effects seem to be minimal.

Subacute eczema

Steroid lotions or creams are the mainstay of treatment; their strength is determined by the severity of the attack. Vioform, bacitracin, fusidic acid, mupirocin or neomycin (see Formulary 1, p. 334) can be incorporated into the application if an infective element is present, but watch out for sensitization to neomycin, especially when treating gravitational eczema.

Chronic eczema

This responds best to steroids in an ointment base, but is also often helped by non-steroid applications such as ichthammol and zinc cream or paste.

The strength of the steroid is important (Fig. 7.6). Nothing stronger than 0.5 or 1% hydrocortisone ointment should be used on the face or in infancy. Even in adults one should be reluctant to prescribe more than 200 g/week of a mildly potent steroid, 50 g/week of a moderately potent or 30 g/week of a potent one for long periods. Very potent topical steroids should not be used long-term.

Fig. 7.6 Stretch marks following the use of too potent topical steroids to the groin.
Bacterial superinfection may need systemic antibiotics but can often be controlled by the incorporation of antibiotics, e.g. fusidic acid, mupirocin, neomycin or chlorotetracycline, or antiseptics, e.g. Vioform, into the steroid formulation. Many proprietary mixtures of this type are available in the UK. Chronic localized hyperkeratotic eczema of the palms or soles can be helped by salicylic acid (1–6% in emulsifying ointment) or stabilized urea preparations (Formulary 1, p. 328).

**Systemic treatment**

Short courses of systemic steroids may occasionally be justified in extremely acute and severe eczema, particularly when the cause is known and already eliminated (e.g. allergic contact dermatitis from a plant such as poison ivy). However, prolonged systemic steroid treatment should be avoided in chronic cases, particularly in atopic eczema. Hydroxyzine, doxepin, trimeprazine and other antihistamines (Formulary 2, p. 344) may help at night. Systemic antibiotics may be needed in widespread bacterial superinfection. However, *Staphylococcus aureus* routinely colonizes all weeping eczemas, and most dry ones as well. Simply isolating it does not automatically prompt a prescription for an antibiotic, although if the density of organisms is high, usually manifest as extensive crusting, then systemic antibiotics can help.

**Common patterns of eczema**

**Irritant contact dermatitis**

This accounts for more than 80% of all cases of contact dermatitis, and for the vast majority of industrial cases. However, it can also occur in children, e.g. as a reaction to a bubble bath, play dough or lip-licking (Fig. 7.7).

**Cause**

Strong irritants elicit an acute reaction after brief contact and the diagnosis is then usually obvious. Prolonged exposure, sometimes over years, is needed for weak irritants to cause dermatitis, usually of the hands and forearms (Fig. 7.8). Detergents, alkalis, solvents, cutting oils and abrasive dusts are common culprits. There is a wide range of susceptibility: those with very dry or fair skins are especially vulnerable. Past or present atopic dermatitis doubles the risk of irritant hand eczema developing.

**Course**

The need to continue at work, or with housework, often stops the skin regaining its normal barrier
function. Even under ideal circumstances this may take several months. All too often therefore irritant eczema, probably reversible in the early stages, becomes chronic.

Complications
The condition may lead to loss of work.

Differential diagnosis
It is often hard to differentiate irritant from allergic contact dermatitis, and from atopic eczema of the hands—the more so as atopic patients are especially prone to develop irritant eczema.

Investigations
Patch testing with irritants is not helpful and may be misleading; but patch testing to a battery of common allergens (p. 35) is worthwhile if an allergic element is suspected. Even if the results are negative, patch testing is not a waste of time, and provides a valuable opportunity to educate patients about their condition.

Treatment
Management is based upon avoidance of the irritants responsible for the condition, but often this is not possible and the best that can be achieved is reduced exposure by the use of protective gloves and clothing. The factory doctor or nurse can often advise here. Washing facilities at work should be good. Barrier creams seldom help established cases, and dirty hands should not be cleaned with harsh solvents.

Prevention is better than cure because, once started, irritant eczema can persist long after contact with offending substances has ceased, despite the vigorous use of emollients and topical corticosteroids. Vulnerable people should be advised to avoid jobs that carry an especially heavy exposure to skin irritants (see Table 7.4). If the right person can be placed in the right job, fewer trainee hairdressers and mechanics will find out the hard way that their skins are easily

Table 7.3 The allergens in our battery and what they mean.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Common sources</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chrome</td>
<td>Cement; chromium plating processes; antirust paints; tattoos (green) and some leathers. Sensitization follows contact with chrome salts rather than chromium metal</td>
<td>A common problem for building site workers. In Scandinavia putting iron sulphate into cement has been shown to reduce its allergenicity by making the chrome salts insoluble</td>
</tr>
<tr>
<td>Nickel</td>
<td>Nickel-plated objects, especially cheap jewellery. Remember jean studs</td>
<td>The best way of becoming sensitive is to pierce your ears. Nickel is being taken out of some good costume jewellery. Stainless steel is relatively safe</td>
</tr>
<tr>
<td>Cobalt</td>
<td>A contaminant of nickel and occurs with it</td>
<td>Eruption similar to that of nickel allergy. The main allergen for those with metal on metal arthroplasties</td>
</tr>
<tr>
<td>Cosmetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragrance mix</td>
<td>An infinite variety of cosmetics, sprays and toiletries</td>
<td>Any perfume will contain many ingredients. This convenient mix picks up some 80% of perfume allergies. Some perfume allergic subjects also react to balsam of Peru, tars or colophony</td>
</tr>
</tbody>
</table>

Continued p. 78
## Table 7.3 (cont’d)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Common sources</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balsam of Peru</td>
<td>Used in some scented cosmetics. Also in some spices and suppositories, e.g. Anusol</td>
<td>May indicate allergy to perfumes also. Can cross-react with colophony, orange peel, cinnamon and benzyl benzoate</td>
</tr>
<tr>
<td>Paraphenylene diamine (PPD)</td>
<td>Dark dyes for hair and clothing</td>
<td>Few heed the manufacturer’s warning to patch test themselves before dyeing their hair. May cross-react with other chemicals containing the ‘para’ group, e.g. some local anaesthetics, sulphonamides or para-aminobenzoic acid (in some sunscreens)</td>
</tr>
<tr>
<td>Wool alcohols</td>
<td>Anything with lanolin in it</td>
<td>Common cause of reactions to cosmetics and topical medicaments. The newer purified lanolins cause fewer problems</td>
</tr>
<tr>
<td>Cetosteryl alcohol</td>
<td>Emollient, and base for many cosmetics</td>
<td>Taking over now as a vehicle from lanolin</td>
</tr>
</tbody>
</table>

**Preservatives and biocides**

No one likes rancid cosmetics, or smelly cutting oils. Biocides are hidden in many materials to stop this sort of thing happening.

| Formaldehyde                    | Used as a preservative in some shampoos and cosmetics. Also in pathology laboratories and white shoes | Many pathologists are allergic to it. Quaternium 15 (see below) releases formaldehyde as do some formaldehyde resins                  |
| Parabens-mix                    | Preservatives in a wide variety of creams and lotions, both medical and cosmetic | Common cause of allergy in those who react to a number of seemingly unrelated creams                                                 |
| Chlorocresol                    | Common preservative                                                           | Cross reacts with chloroxylenol—a popular antiseptic                                                                                |
| Kathon                          | Preservative in many cosmetics, shampoos, soaps and sunscreens                | Also found in some odd places such as moist toilet papers, and washing-up liquids                                                      |
| Quaternium 15                  | Preservative in many topical medicaments and cosmetics                        | Releases formaldehyde and may cross-react with it                                                                                     |
| Imidazolidinyl urea             | Common ingredient of moisturizers and cosmetics                               | Cosmetic allergy                                                                                                                      |
| Other biocides                  | In glues, paints, cutting oils, etc.                                          | Responsible for some cases of occupational dermatitis                                                                               |

**Medicaments**

These may share allergens, such as preservatives and lanolin, with cosmetics (see above). In addition the active ingredients can sensitize, especially when applied long-term to venous ulcers, pruritus ani, eczema or otitis externa.

| Neomycin                        | Popular topical antibiotic. Safe in short bursts, e.g. for impetigo and cuts | Common sensitizer in those with leg ulcers. Simply swapping to another antibiotic may not always help as neomycin cross-reacts with framycetin and gentamycin |
| Quinoline mix                   | Used as an antiseptic in creams, often in combination with a corticosteroid  | Its aliases include Vioform and chinoform                                                                                              |
| Ethylenediamine dihydrochloride | Stabilizer in some topical steroid mixtures (e.g. Mycolog and the alleged active ingredient in fat removal creams). A component in aminophylline. A hardener for epoxy resin | Cross-reacts with some antihistamines, e.g. hydroxyzine                                                                                   |
### Table 7.3 (cont’d)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Common sources</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td>A local anaesthetic which lurks in some topical applications, e.g. for piles and sunburn</td>
<td>Dermatologists seldom recommend using these preparations—they have seen too many reactions</td>
</tr>
<tr>
<td>Tixocortol pivalate</td>
<td>Topical steroid</td>
<td>A marker for allergy to various topical steroids. Hydrocortisone allergy exists. Think of this when steroid applications seem to be making things worse</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Topical steroid</td>
<td>Testing with both tixocortol pivalate and budesonide will detect 95% of topical steroid allergies</td>
</tr>
</tbody>
</table>

### Rubber

Rubber itself is often not the problem: but it has to be converted from soft latex (p. 96) to usable rubber by adding vulcanizers to make it harder, accelerators to speed up vulcanization, and antioxidants to stop it perishing in the air. These additives are allergens

- **Mercapto-mix**: Chemicals used to harden rubber. Diagnosis is often obvious: sometimes less so. Remember shoe soles, rubber bands and golf club grips.
- **Thiuram-mix**: Another set of rubber accelerators. Common culprit in rubber glove allergy.
- **Black rubber mix**: All black heavy-duty rubber, e.g. tyres, rubber boots, squash balls. These are paraphenylene diamine derivatives, cross-reacting with PPD dyes (see above).
- **Carba mix**: Mainly in rubber gloves. Patch testing with rubber chemicals occasionally sensitizes patients to them.

### Plants

In the USA, the Rhus family (poison ivy and poison oak) are important allergens: in Europe, *Primula obconica* holds pride of place. Both cause severe reactions with streaky erythema and blistering. The Rhus antigen is such a potent sensitizer that patch testing with it is unwise. Other reaction patterns include a lichenified dermatitis of exposed areas from chrysanthemums, and a fingertip dermatitis from tulip bulbs.

- **Primin**: Allergen in *Primula obconica*. More reliable than patch testing to *Primula* leaves.
- **Sesquiterpene lactone mix**: Compositae plant allergy. Picks up chrysanth allergy. Flying pollen affects exposed parts and reactions can look like light sensitivity.

### Resins

Common sensitizers such as epoxy resins can cause trouble both at home, as adhesives, and in industry.

- **Epoxy resin**: Common in ‘two-component’ adhesive mixtures (e.g. Araldite). Also used in electrical and plastics industries. ‘Cured’ resin does not sensitize. A few become allergic to the added hardener rather than to the resin itself.
- **Paratertiary butylphenol formaldehyde resin**: Used as an adhesive, e.g. in shoes, wrist watch straps, prosthesis, hobbies. Cross-reacts with formaldehyde. Depigmentation has been recorded.
- **Colophony**: Naturally occurring and found in pine sawdust. Used as an adhesive in sticking plasters, bandages. Also found in various varnishes, paper and rosin. The usual cause of sticking plaster allergy; also of dermatitis of the hands of violinists who handle rosin.
irritated. Moderately potent topical corticosteroids and emollients are valuable, but are secondary to the avoidance of irritants and protective measures.

Allergic contact dermatitis

Cause
The mechanism is that of delayed (type IV) hypersensitivity, which is dealt with in detail on p. 26. It has the following features.
• Previous contact is needed to induce allergy.
• It is specific to one chemical and its close relatives.
• After allergy has been established, all areas of skin will react to the allergen.
• Sensitization persists indefinitely.
• Desensitization is seldom possible.

Allergens
In an ideal world, allergens would be replaced by less harmful substances, and some attempts are already being made to achieve this. A whole new industry has arisen around the need for predictive patch testing before new substances or cosmetics are let out into the community. Similarly, chrome allergy is less of a problem now in enlightened countries that insist on adding ferrous sulphate to cement to reduce its water-soluble chromate content. However, contact allergens will never be abolished completely and family doctors still need to know about the most common ones and where to find them (Table 7.3). It is not possible to guess which substances are likely to sensitize just by looking at their formulae. In fact, most allergens are relatively simple chemicals that have to bind to protein to become ‘complete’ antigens. Their ability to sensitize varies—from substances that can do so after a single exposure (e.g. poison ivy), to those that need prolonged exposure (e.g. chrome—bricklayers take an average of 10 years to become allergic to it).

Presentation and clinical course
The original site of the eruption gives a clue to the likely allergen but secondary spread may later obscure this. Easily recognizable patterns exist. Nickel allergy, for example, gives rise to eczema under jewellery, bra clips and jean studs (Fig. 7.9). The lax skin of the eyelids and genitalia is especially likely to become oedematous. Possible allergens are numerous and to spot the less common ones in the environment needs specialist knowledge. Table 7.3 lists some common allergens and their distribution.

Allergic contact dermatitis should be suspected if:
1 certain areas are involved, e.g. the eyelids, external auditory meati, hands (Fig. 7.10) or feet, and around gravitational ulcers;
2 there is known contact with the allergens mentioned in Table 7.3; or
3 the individual’s work carries a high risk, e.g. hairdressing, working in a flower shop, or dentistry.
Investigations

Questioning should cover both occupational and domestic exposure to allergens. The indications for patch testing have already been discussed on p. 35. Techniques are constantly improving and dermatologists will have access to a battery of common allergens, suitably diluted in a bland vehicle. These are applied in aluminium cups held in position on the skin for 2 or 3 days by tape. Patch testing will often start with a standard series (battery) of allergens whose selection is based on local experience. Table 7.3 shows the battery we use and how it helps us with the most common types of contact allergy. This picks up some 80% of reactions. Extra series of relevant allergens will be used for problems such as hand eczema, leg ulcers and suspected cosmetic allergy, and for those in jobs like dentistry or hairdressing, which carry unusual risks. Some allergies are more common than others: in most centres, nickel tops the list, with a positive reaction in some 15% of those tested; fragrance allergy usually comes second. It is important to remember that positive reactions are not necessarily relevant to the patient’s current skin problem: some are simply ‘immunological scars’ left behind by previous unrelated problems.

Treatment

Topical corticosteroids give temporary relief, but far more important is avoidance of the relevant allergen. Reducing exposure is usually not enough: active steps have to be taken to avoid the allergen completely. Job changes are sometimes needed to achieve this. Even then, other factors may come into play; e.g. some believe that reactions to nickel can be kept going by nickel in the diet, released from cans or steel saucepans, as changes in diet and cooking utensils may rarely be helpful.

Occupational dermatitis

The size of this problem has been underestimated in the past but, both in the UK and the USA, dermatitis is the second most common occupational disorder—second only to musculoskeletal injuries. In the UK, it is most common in younger women (Fig. 7.11), and then is often associated with wet work. The incidence in men rises with age, and in older workers it is often caused by contact with cutting oils. Table 7.4 lists the types of work particularly associated with high rates of contact dermatitis in the UK. The hands are affected in 80–90% of cases. Often several factors (constitutional, irritant and allergic) have combined to cause this, and a change of job does not always lead to a cure, particularly in long-established cases. In one large series, hand dermatitis was most common in caterers, metal workers, hairdressers, health care workers and mechanics.

Atopic eczema

The word ‘atopy’ comes from the Greek (a-topos: ‘without a place’). It was introduced by Coca and
CHAPTER 7

members will have eczema; in others respiratory allergy will predominate. There is also a tendency for atopic diseases to be inherited more often from the mother than the father. Environmental factors too are important and, not surprisingly, a simple genetic explanation has not yet been found.

Probably the inheritance of atopic eczema requires genes that predispose to the state of atopy itself, and others that determine whether it is asthma, eczema or hay fever that occurs. One plausible gene for the inheritance of atopy itself lies on chromosome 11q13. It encodes for the E subunit of the high affinity IgE receptor, which is found both on mast cells (Fig. 8.1) and on antigen-presenting cells in the skin. However, it has to be pointed out that several groups have failed to confirm this linkage either in the families of those with atopic eczema or respiratory allergy. Most recently, another gene strongly linked to atopic eczema has been found on chromosome 3q21. It encodes for cluster of differentiation (CD) antigens 80 and 86. Other candidates lie on chromosomes 14q, 16p and 17p.

Presentation and course

Seventy-five per cent of cases of atopic eczema begin before the age of 6 months, and 80–90% before the age of 5 years. It affects at least 3% of infants, but the onset may be delayed until childhood or adult life. Some 60–70% of children with atopic eczema will clear by their early teens, although subsequent relapses are possible. The distribution and character of the lesions vary with age (Fig. 7.12) but a general dryness of the skin may persist throughout life.

• In infancy, atopic eczema tends to be vesicular and weeping. It often starts on the face (Fig. 7.13) with a non-specific distribution elsewhere, commonly sparing the napkin (diaper) area.

• In childhood, the eczema becomes leathery, dry and excoriated, affecting mainly the elbow and knee flexures (Fig. 7.14), wrists and ankles. A stubborn ‘reverse’ pattern affecting the extensor aspects of the limbs is also recognized.

• In adulthood, the eczema becomes leathery, dry and excoriated, affecting mainly the elbow and knee flexures (Fig. 7.14), wrists and ankles. A stubborn ‘reverse’ pattern affecting the extensor aspects of the limbs is also recognized.

Inheritance

A strong genetic component is obvious, although affected children can be born to clinically normal parents. The concordance rates for atopic eczema in monozygotic and dizygotic twins are 86% and 21%, respectively; and atopic diseases tend to run true to type within each family. In some, most of the affected

Cooke in 1923 and refers to the lack of a niche in the medical classifications then in use for the grouping of asthma, hay fever and eczema. Atopy is a state in which an exuberant production of IgE occurs as a response to common environmental allergens. Atopic subjects may, or may not, develop one or more of the atopic diseases such as asthma, hay fever, eczema and food allergies, and the prevalence of atopy is steadily rising.

In Scotland, as many as 8% of children under 2 years have visible atopic eczema. At least 1 school-child in 10 in Europe now suffers from atopic eczema and this figure is still rising. The reasons for this are not yet clear, but are unlikely to be a change in the genetic pool in the population. However, several environmental factors have been shown to reduce the risk of developing atopic disease. These include having many older siblings, growing up on a farm, having childhood measles and gut infections. The ‘hygiene hypothesis’ unites these, blaming changes in infant diets, the early use of antibiotics and a reduced exposure to orofaecal and other infections for preventing normal immunological maturation. The subsequent understimulation of gut-associated lymphoid tissue may predispose to atopic sensitization to environmental allergens. The circulating T lymphocytes of children destined to develop allergies shift to a type II response (see Chapter 2) and are poor at producing γ-interferon (IFN-γ); this persists into late childhood. Early infections may lower the risk of allergy by boosting the production of INF-γ.

One promising but still experimental way of tackling these problems has emerged recently, involving the use of probiotics, which are cultures of potentially beneficial bacteria. They may reverse the increased intestinal permeability that is characteristic of children with atopic eczema. In one recent study, the perinatal administration of a Gram-positive probiotic (Lactobacillus GG) halved the subsequent occurrence of eczema in at-risk infants.

Presentation and course

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Diagnostic criteria

Useful diagnostic criteria have been developed in the UK recently (Table 7.5).

Fig. 7.12 The pattern of atopic eczema varies with age. It may clear at any stage.

Iatrogenic picture. Affected children may sleep poorly, be hyperactive and sometimes manipulative, using the state of their eczema to get what they want from their parents. Luckily, the condition remits spontaneously before the age of 10 years in at least two-thirds of affected children, although it may come back at times of stress. Eczema and asthma may seesaw, so that while one improves the other may get worse.
Complications

Overt bacterial infection is troublesome in many patients with atopic eczema (Fig. 7.16). They are also especially prone to viral infections, most dangerously with widespread herpes simplex (eczema herpeticum; Fig. 7.17), but also with molluscum contagiosum and warts. Growth hormone levels rise during deep sleep (stages 3 and 4), but these stages may not be reached during the disturbed sleep of children with severe atopic eczema and as a consequence they may grow poorly. The absorption of topical steroids can contribute to this too.

Table 7.5  Diagnostic criteria for atopic eczema.

<table>
<thead>
<tr>
<th>Must have:</th>
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<tr>
<td>A chronically itchy skin (or report of scratching or rubbing in a child)</td>
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<table>
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<tr>
<th>Plus three or more of the following:</th>
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<tr>
<td>History of itchiness in skin creases such as folds of the elbows, behind the knees, fronts of ankles or around the neck (or the cheeks in children under 4 years)</td>
</tr>
<tr>
<td>History of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4 years)</td>
</tr>
<tr>
<td>General dry skin in the past year</td>
</tr>
<tr>
<td>Visible flexural eczema (or eczema affecting the cheeks or forehead and outer limbs in children under 4 years)</td>
</tr>
<tr>
<td>Onset in the first 2 years of life (not always diagnostic in children under 4 years)</td>
</tr>
</tbody>
</table>
Investigations

Prick testing (see Fig. 3.10) demonstrates immediate-type hypersensitivity and is helpful in the investigation of asthma and hay fever. However, the value of prick testing in atopic eczema remains controversial. Often the finding of multiple positive reactions, and a high IgE level, does little more than support a doubtful clinical diagnosis without leading to fruitful lines of treatment.

Treatment

Management here is complex and should include the following.

• Explanation, reassurance and encouragement. Many patients and parents benefit from an introduction to the National Eczema Society in the UK or the National Eczema Association for Science and Education or the Inflammatory Skin Institute in the USA.

• The avoidance of exacerbating factors such as irritants (e.g. woollen clothing next to the skin) and later of careers such as hairdressing and engineering, which would inevitably lead to much exposure to irritants. Also avoid extremes of temperature, and contact with soaps and detergents.

• The judicious use of topical steroids and other applications as for other types of chronic eczema (p. 75 and Table 7.6). A technique useful for extensive and troublesome eczema, particularly in children, is that of ‘wet wrap’ dressings—see above (p. 75). A nurse who is expert in applying such dressings is an asset to any practice (Fig. 7.18).

Tacrolimus (Formulary 1, p. 334) is a macrolide immunosuppressant produced by a streptomycete. It is used systemically in kidney, liver and heart transplantation. Trials of tacrolimus in ointment form have shown that it can be a quick and highly successful topical treatment for moderate to severe atopic eczema. The preparation seems to be safe in use, with a

Table 7.6 Principles of treatment with topical corticosteroids.

Use the weakest steroid that controls the eczema effectively
Review their use regularly: check for local and systemic side-effects
In primary care, avoid using potent and very potent steroids for children with atopic eczema
Be wary of repeat prescriptions
transient burning sensation being the most common side-effect; however, it decreases with usage. Some use topical steroids briefly, to improve the eczema, before starting tacrolimus ointment, hoping in this way to decrease the incidence and severity of this burning sensation. Systemic absorption is low, and skin atrophy is not a problem. Local infection might be troublesome and the development of skin cancer, especially on exposed treated areas, is a concern when the drug is used for prolonged periods. Perhaps more information and experience are required before tacrolimus can be hailed as a revolutionary new treatment for the treatment of inflammatory skin disorders—but the results so far look highly impressive. Topical tacrolimus is now available as Protopic ointment (Formulary 1, p. 334).

Pimecrolimus (Formulary 1, p. 334) is another topical immunosuppressant and a derivative of askamycin. Clinical trials in moderate atopic eczema have been encouraging and it can be used in patients older than 3 months. Its action is very similar to that of tacrolimus and time will tell if either preparation is superior.

- The regular use of bland emollients, either directly to the skin or in the form of oils to be used in the bath. Some of these can also be used as soap substitutes. A list of suitable preparations is given in Formulary 1 (p. 328). Some rules governing the use of emollients are given in Table 7.7.
- Those with an associated ichthyosis should generally use ointments rather than creams.
- The scratch–itch cycle can often be interrupted by occlusive bandaging, e.g. with a 1% ichthammol paste bandage. Nails should be kept short.

Table 7.7 Winning ways with emollients.

| Make sure they are applied when the skin is moist |
| Prescribe plenty (at least 500 g/week for the whole skin of an adult and 250 g/week for the whole skin of a child) and ensure they are used at least 3–4 times a day |
| For maximal effect, combine the use of creams, ointments, bath oils and emollient soap substitutes |

- Sedative antihistamines, e.g. trimeprazine or hydroxyzine (Formulary 2, p. 345) are of value if sleep is interrupted, but histamine release is not the main cause of the itching, so the newer non-sedative antihistamines help less than might be expected.
- Acute flares are often induced by the surface proliferation of staphylococci, even without frank sepsis. A month’s course of a systemic antibiotic, e.g. erythromycin, may then be helpful.
- Allergen avoidance: prick tests confirm that most sufferers from atopic eczema have immediate hypersensitivity responses to allergens in the faeces of house dust mites. Sometimes, but not always, measures to reduce contact with these allergens help eczema. These measures should include encasing the mattress in a dustproof bag, washing the duvets and pillows every 3 months at a temperature greater than 55°C, and thorough and regular vacuuming in the bedroom, where carpets should preferably be avoided.
- Do not keep pets to which there is obvious allergy.
- The role of diet in atopic eczema is even more debatable, and treatments based on changing the diet of sufferers are often disappointing. Similarly, it is not certain that the avoidance of dietary allergens (e.g. cow’s milk and eggs) by a pregnant or lactating woman lessens the risk of her baby developing eczema. It may still be wise to breastfeed children at special risk for 6 months.
- Routine inoculations are permissible during quiet phases of the eczema. However, children who are allergic to eggs should not be inoculated against measles, influenza and yellow fever.
- Those with active herpes simplex infections should be avoided to cut the risk of developing eczema herpeticum.
- In stubborn cases UVB, UVA-1 (340–400 nm) or even PUVA therapy may be useful.
- Cyclosporin: severe and unresponsive cases may be helped by short courses under specialist supervision (Formulary 2, p. 347).
Seborrhoeic eczema

Presentation and course

The term covers at least three common patterns of eczema, mainly affecting hairy areas, and often showing characteristic greasy yellowish scales. These patterns may merge together (Fig. 7.19).

1 A red scaly or exudative eruption of the scalp, ears (Fig. 7.20), face (Fig. 7.21) and eyebrows. May be associated with chronic blepharitis and otitis externa.

2 Dry scaly ‘petaloid’ lesions of the presternal (Fig. 7.22) and interscapular areas. There may also be extensive follicular papules or pustules on the trunk (seborrhoeic folliculitis or pityrosporum folliculitis).

- Chinese herbal remedies: properly conducted trials have given promising results but difficulties remain. The active ingredients within these complex mixtures of herbs have still not been identified. We have some hope for the future but currently do not prescribe these treatments for our patients.

LEARNING POINT

Do not encourage cranky dieting for atopic eczema: it causes anxiety and seldom if ever does much good.
Intertriginous lesions of the armpits, umbilicus or groins, or under spectacles or hearing aids.

Cause

This condition is not obviously related to seborrhoea. It may run in some families, often affecting those with a tendency to dandruff. The success of treatments directed against yeasts has suggested that overgrowth of the pityrosporum yeast skin commensals plays an important part in the development of seborrhoeic eczema. This fits well with the fact that seborrhoeic eczema is often an early sign of AIDS, and that it responds to antiyeast agents such as topical ketoconazole shampoo or cream.

Seborrhoeic eczema may affect infants (Fig. 7.23) but is most common in adult males. In infants it clears quickly but in adults its course is unpredictable and may be chronic or recurrent. Some particularly severe
cases have occurred in patients with AIDS (p. 211 and Fig. 14.35).

Complications
May be associated with furunculosis. In the intertriginous type, superadded Candida infection is common.

Investigations
None are usually needed, but bear possible HIV infection and Parkinson’s disease in mind.

Treatment
Therapy is suppressive rather than curative and patients should be told this. Topical imidazoles (Formulary 1, p. 335) are perhaps the first line of treatment. Two per cent sulphur and 2% salicylic acid in aqueous cream is often helpful and avoids the problem of topical steroids. It may be used on the scalp overnight and removed by a medicated shampoo, which may contain ketoconazole, tar, salicylic acid, sulphur, zinc or selenium sulphide (Formulary 1, p. 329). A topical lithium preparation (Formulary 1, p. 339) may help the facial rash. For intertriginous lesions a weak steroid–antiseptic or steroid–antifungal combination (Formulary 1, p. 332) is often effective. For severe and unresponsive cases a short course of oral itraconazole may be helpful.

Discoid (nummular) eczema

Cause
No cause has been established but chronic stress is often present. A reaction to bacterial antigens has been suspected as the lesions often yield staphylococci on culture, and as steroid–antiseptic or steroid–antibiotic mixtures do better than either separately.

Presentation and course
This common pattern of endogenous eczema classically affects the limbs of middle-aged males. The lesions are multiple, coin-shaped, vesicular or crusted, highly itchy plaques (Fig. 7.24), usually less than 5 cm across. The condition tends to persist for many months, and recurrences often appear at the site of previous plaques.

Fig. 7.24 Vesicular and weeping patch of discoid eczema.

Investigations
None are usually needed.

Treatment
With topical steroid–antiseptic or steroid–antibiotic combinations (see above).

Pompholyx

Cause
The cause is usually unknown, but pompholyx is sometimes provoked by heat or emotional upsets. In subjects allergic to nickel, small amounts of nickel in food may trigger pompholyx. The vesicles are not plugged sweat ducts, and the term ‘dyshidrotic eczema’ should now be dropped.

Presentation and course
In this tiresome and sometimes very unpleasant form of eczema, recurrent bouts of vesicles or larger blisters appear on the palms, fingers (Fig. 7.25) and/or the soles of adults. Bouts lasting a few weeks recur at
irregular intervals. Secondary infection and lymphangitis are a recurrent problem for some patients.

Investigations

None are usually needed: sometimes a pompholyx-like eruption of the hands can follow acute tinea pedis (an ide reaction). If this is suspected, scrapings or blister roofs, not from the hand lesions but from those on the feet, should be sent for mycological examination. Swabs from infected vesicles should be cultured for bacterial pathogens.

Treatment

As for acute eczema of the hands and feet (p. 75). Appropriate antibiotics should be given for bacterial infections. Aluminium acetate or potassium permanganate soaks, followed by applications of a very potent corticosteroid cream, are often helpful.

Asteatotic eczema

Cause

Many who develop asteatotic eczema in old age will always have had a dry skin and a tendency to chap.
Localized neurodermatitis (lichen simplex)

Cause
The skin is damaged as a result of repeated rubbing or scratching, as a habit or in response to stress, but there is no underlying skin disorder.

Presentation and course
Usually occurs as a single fixed itchy lichenified plaque (Fig. 7.28). Favourite areas are the nape of the neck in women, the legs in men, and the anogenital area in both sexes. Lesions may resolve with treatment but tend to recur either in the same place or elsewhere.

Investigations
None are usually needed.

Treatment
Potent topical steroids or occlusive bandaging, where feasible, help to break the scratch–itch cycle. Tranquillizers are often disappointing.

Juvenile plantar dermatosis (Fig. 7.29)

Cause
This condition is thought to be related to the impermeability of modern socks and shoe linings with other contributory factors including the removal of surface lipids by over-washing, the low humidity of winter and central heating, the use of diuretics, and hypothyroidism.

Presentation and course
Often unrecognized, this common and itchy pattern of eczema occurs usually on the legs of elderly patients. Against a background of dry skin, a network of fine red superficial fissures creates a ‘crazy paving’ appearance (Fig. 7.27).

Investigations
None are usually needed. Very extensive cases may be part of malabsorption syndromes, zinc deficiency or internal malignancy.

Treatment
Can be cleared by the use of a mild or moderately potent topical steroid in a greasy base, and aqueous cream as a soap substitute for the area. Baths should be restricted until clearance. Thereafter, daily use of unmedicated emollients (Formulary 1, p. 328) usually prevents recurrence.
Napkin (diaper) dermatitis

Cause
The most common type of napkin eruption is irritant in origin, and is aggravated by the use of waterproof plastic pants. The mixture of faecal enzymes and ammonia produced by urea-splitting bacteria, if allowed to remain in prolonged contact with the skin, leads to a severe reaction. The overgrowth of yeasts is another aggravating factor. The introduction of modern disposable napkins has, over the last few years, helped to reduce the number of cases sent to our clinics.

Presentation
The moist, often glazed and sore erythema affects the napkin area generally (Fig. 7.30), with the exception of the skin folds, which tend to be spared.

Complications
Superinfection with *Candida albicans* is common, and this may lead to small erythematous papules or vesicopustules appearing around the periphery of the main eruption.

Differential diagnosis
The sparing of the folds helps to separate this condition from infantile seborrhoeic eczema and candidiasis.

Treatment
It is never easy to keep this area clean and dry, but this is the basis of all treatment. Theoretically, the child should be allowed to be free of napkins as much as possible but this may lead to a messy nightmare. On both sides of the Atlantic disposable nappies (diapers) have largely replaced washable ones. The superabsorbent type is best and should be changed regularly, especially in the middle of the night. When towelling napkins are used they should be washed thoroughly and changed frequently. The area should be cleaned at each nappy change with aqueous cream and water. Protective ointments, e.g., zinc and castor oil ointment, or silicone protective ointments, are often useful subsequent sweat gland blockage, and so has been called the ‘toxic sock syndrome’! Some feel the condition is a manifestation of atopy.

Presentation and course
The skin of the weight-bearing areas of the feet, particularly the forefeet and undersides of the toes, becomes dry and shiny with deep painful fissures that make walking difficult. The toe webs are spared. Onset can be at any time after shoes are first worn, and even if untreated the condition clears in the early teens.

Investigations
Much time has been wasted in patch testing and scraping for fungus.

Treatment
The child should use a commercially available cork insole in all shoes, and stick to cotton or wool socks. An emollient such as emulsifying ointment or 1% ichthammol paste, or an emollient containing lactic acid, is as good as a topical steroid.
(Formulary 1, p. 331), as are topical imidazole preparations that stop yeast growth. Potent steroids should be avoided but combinations of hydrocortisone with antifungals or antiseptics (Formulary 1, p. 332) are often useful.

**Further reading**


**LEARNING POINTS**

1. Do not accept ‘eczema’ as an adequate diagnosis: treatment hinges on establishing its cause and type.
2. Keep fluorinated steroids off the face of adults and off the skin of infants.
3. Monitor repeat prescriptions of topical steroids, keeping an eye on the amount used and their potency.
4. Do not promise that atopic eczema will be clear by any particular age: guesses are always wrong and the patients lose faith.
Blood vessels can be affected by a variety of insults, both exogenous and endogenous. When this occurs, the epidermis remains unaffected, but the skin becomes red or pink and often oedematous. This is a reactive erythema. If the blood vessels are damaged more severely, as in vasculitis, purpura or larger areas of haemorrhage mask the erythematos colour.

**Urticaria (hives, ‘nettle-rash’)**

Urticaria is a common reaction pattern in which pink, itchy or ‘burning’ swellings (wheals) can occur anywhere on the body. Individual wheals do not last longer than 24 h, but new ones may continue to appear for days, months or even years. Traditionally, urticaria is divided into acute and chronic forms, based on the duration of the disease rather than of individual wheals. Urticaria that persists for more than 6 weeks is classified as chronic. Most patients with chronic urticaria, other than those with an obvious physical cause, have what is often known as ‘ordinary urticaria’.

**Cause**

The signs and symptoms of urticaria are caused by mast cell degranulation, with release of histamine (Fig. 8.1). The mechanisms underlying this may be
Solar urticaria
Wheals occur within minutes of sun exposure. Some patients with solar urticaria have erythropoietic protoporphyria (p. 287); most have an IgE-mediated urticarial reaction to sunlight.

Heat urticaria
In this condition wheals arise in areas after contact with hot objects or solutions.

Cholinergic urticaria
Anxiety, heat, sexual excitement or strenuous exercise elicits this characteristic response. The vessels overreact to acetylcholine liberated from sympathetic nerves in the skin. Transient 2–5 mm follicular macules or papules (Fig. 8.2) resemble a blush or viral exanthem. Some patients get blotchy patches on their necks.

Dermographism (Fig. 8.3)
This is the most common type of physical urticaria, the skin mast cells releasing extra histamine after rubbing or scratching. The linear wheals are therefore an exaggerated triple response of Lewis. They can readily be reproduced by rubbing the skin of the back lightly at different pressures, or by scratching the back with a fingernail or blunt object.

Delayed pressure urticaria
Sustained pressure causes oedema of the underlying skin and subcutaneous tissue 3–6 h later. The swelling
CHAPTER 8

FcßE receptors on mast cells. Here the autoantibody acts as antigen to trigger mast cell degranulation.

Pharmacological urticaria

This occurs when drugs cause mast cells to release histamine in a non-allergic manner (e.g. aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and morphine).

Contact urticaria

This may be IgE-mediated or caused by a pharmacological effect. Wheals occur most often around the mouth. Foods and food additives are the most common culprits but drugs, animal saliva, caterpillars and plants may cause the reaction. Recently, latex allergy has become a significant public health concern.

Latex allergy

Possible reactions to the natural rubber latex of the *Hevea brasiliensis* tree include irritant dermatitis, contact allergic dermatitis (Chapter 7) and type I allergy (Chapter 2). Reactions associated with the latter include hypersensitivity urticaria (both by contact and by inhalation), hay fever, asthma, anaphylaxis and, rarely, death.

Medical latex gloves became universally popular after precautions were introduced to protect against HIV and hepatitis B infections. The demand for the gloves increased and this led to alterations in their manufacture and to a flood of high allergen gloves on the market. Cornstarch powder in these gloves bound to the latex proteins so that the allergen became airborne when the gloves were put on. Individuals at increased risk of latex allergy include health care workers, those undergoing multiple surgical procedures (e.g. spina bifida patients) and workers in mechanical, catering and electronic trades. Around 1–6% of the general population is believed to be sensitized to latex.

Latex reactions should be treated on their own merits (see below for urticaria, p. 312 and Fig. 22.5 for anaphylaxis and Chapter 7 for dermatitis). Prevention of latex allergy is equally important. Non-latex (e.g. vinyl) gloves should be worn by those not handling infectious material (e.g. caterers) and, if latex gloves are chosen for those handling infectious material, then powder-free low allergen ones should be used.

Other types of urticaria

Hypersensitivity urticaria

This common form of urticaria is caused by hypersensitivity, often an IgE-mediated (type I) allergic reaction (Chapter 2). Allergens may be encountered in ten different ways (the 10 ‘I’s listed in Table 8.2).

Autoimmune urticaria

Some patients with chronic urticaria have an autoimmune disease with IgG antibodies to IgE or to FcßE receptors on mast cells. Here the autoantibody acts as antigen to trigger mast cell degranulation.

Pharmacological urticaria

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This may be IgE-mediated or caused by a pharmacological effect. Wheals occur most often around the mouth. Foods and food additives are the most common culprits but drugs, animal saliva, caterpillars and plants may cause the reaction. Recently, latex allergy has become a significant public health concern.

Latex allergy

Possible reactions to the natural rubber latex of the *Hevea brasiliensis* tree include irritant dermatitis, contact allergic dermatitis (Chapter 7) and type I allergy (Chapter 2). Reactions associated with the latter include hypersensitivity urticaria (both by contact and by inhalation), hay fever, asthma, anaphylaxis and, rarely, death.

Medical latex gloves became universally popular after precautions were introduced to protect against HIV and hepatitis B infections. The demand for the gloves increased and this led to alterations in their manufacture and to a flood of high allergen gloves on the market. Cornstarch powder in these gloves bound to the latex proteins so that the allergen became airborne when the gloves were put on. Individuals at increased risk of latex allergy include health care workers, those undergoing multiple surgical procedures (e.g. spina bifida patients) and workers in mechanical, catering and electronic trades. Around 1–6% of the general population is believed to be sensitized to latex.

Latex reactions should be treated on their own merits (see below for urticaria, p. 312 and Fig. 22.5 for anaphylaxis and Chapter 7 for dermatitis). Prevention of latex allergy is equally important. Non-latex (e.g. vinyl) gloves should be worn by those not handling infectious material (e.g. caterers) and, if latex gloves are chosen for those handling infectious material, then powder-free low allergen ones should be used.

Other types of urticaria

Hypersensitivity urticaria

This common form of urticaria is caused by hypersensitivity, often an IgE-mediated (type I) allergic reaction (Chapter 2). Allergens may be encountered in ten different ways (the 10 ‘I’s listed in Table 8.2).

Autoimmune urticaria

Some patients with chronic urticaria have an autoimmune disease with IgG antibodies to IgE or to

Table 8.2 The 10 ‘I’s of antigen encounter in hypersensitive urticaria.

<table>
<thead>
<tr>
<th>Ingestion</th>
<th>Inhalation</th>
<th>Instillation</th>
<th>Injection</th>
<th>Insertion</th>
<th>Insect bites</th>
<th>Infestations</th>
<th>Infection</th>
<th>Infusion</th>
<th>Inunction (contact)</th>
</tr>
</thead>
</table>

Fig. 8.3 Dermographism: a frenzy of scratching by an already dermographic individual led to this dramatic appearance.

may last up to 48 h and kinins or prostaglandins rather than histamine probably mediate it. It occurs particularly on the feet after walking, on the hands after clapping and on the buttocks after sitting. It can be disabling for manual labourers.

Other types of urticaria

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<th>Infestations</th>
<th>Infection</th>
<th>Infusion</th>
<th>Inunction (contact)</th>
</tr>
</thead>
</table>
Course

The course of an urticarial reaction depends on its cause. If the urticaria is allergic, it will continue until the allergen is removed, tolerated or metabolized. Most such patients clear up within a day or two, even if the allergen is not identified. Urticaria may recur if the allergen is met again. At the other end of the scale, only half of patients attending hospital clinics with chronic urticaria and angioedema will be clear 5 years later. Those with urticarial lesions alone do better, half being clear after 6 months.

Complications

Urticaria is normally uncomplicated, although its itch may be enough to interfere with sleep or daily activities and to lead to depression. In acute anaphylactic reactions, oedema of the larynx may lead to asphyxiation, and oedema of the tracheo-bronchial tree may lead to asthma.

Presentation

Most types of urticaria share the sudden appearance of pink itchy wheals, which can come up anywhere on the skin surface (Figs 8.4 and 8.5). Each lasts for less than a day, and most disappear within a few hours. Lesions may enlarge rapidly and some resolve centrally to take up an annular shape. In an acute anaphylactic reaction, wheals may cover most of the skin surface. In contrast, in chronic urticaria only a few wheals may develop each day.

Angioedema is a variant of urticaria that primarily affects the subcutaneous tissues, so that the swelling is less demarcated and less red than an urticarial wheal. Angioedema most commonly occurs at junctions between skin and mucous membranes (e.g. peri-orbital, peri-oral and genital; Fig. 8.6). It may be associated with swelling of the tongue and laryngeal mucosa. It sometimes accompanies chronic urticaria and its causes may be the same.

Differential diagnosis

There are two aspects to the differential diagnosis of urticaria. The first is to tell urticaria from other eruptions that are not urticaria at all. The second is to define the type of urticaria, according to Table 8.1. Insect bites or stings (Fig. 8.7) and infestations commonly elicit urticarial responses, but these may have a central punctum and individual lesions may last longer than 24 h. Erythema multiforme can mimic an annular urticaria. A form of vasculitis (urticarial vasculitis, p. 103) may resemble urticaria, but individual lesions last for longer than 24 h and may leave
Almost invariably, more is learned from the history than from the laboratory. The history should include details of the events surrounding the onset of the eruption. A review of systems may uncover evidence of an underlying disease. Careful attention should be paid to drugs, remembering that self-prescribed ones can also cause urticaria. Over-the-counter medications (such as aspirin and herbal remedies) and medications given by other routes (Table 8.2) can produce wheals.

If a patient has acute urticaria and its cause is not obvious, investigations are often deferred until it has persisted for a few weeks; then a physical examination (if not already carried out) and screening tests such as a complete blood count, erythrocyte sedimentation rate (ESR), routine biochemical screen, chest X-ray and urine analysis are worthwhile. If the urticaria continues for 2–3 months, the patient should probably be referred to a dermatologist for further evaluation. In general, the focus of such investigations will be on internal disorders associated with urticaria (Table 8.3) and on external allergens (Table 8.4). Even after extensive evaluation and environmental change, the cause cannot always be found.

### Table 8.3 Some endogenous causes of urticaria.

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
</tr>
<tr>
<td>Viral (e.g. hepatitis, infectious mononucleosis, HIV infection during seroconversion)</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td>Mycoplasma</td>
</tr>
<tr>
<td><strong>Intestinal parasites</strong></td>
</tr>
<tr>
<td><strong>Connective tissue disorders</strong></td>
</tr>
<tr>
<td><strong>Hypereosinophilic syndrome</strong> (unexplained eosinophilia with multiple internal organ involvement, especially cardiac)</td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
</tr>
<tr>
<td><strong>Lymphomas</strong></td>
</tr>
</tbody>
</table>

**Hereditary angioedema**

Recurrent attacks of abdominal pain and vomiting, or massive oedema of soft tissues, which may involve the larynx, characterize this autosomal dominant condition. Urticaria does not accompany the tissue swellings. Tooth extraction, cheek biting and other forms of trauma may precipitate an attack. A deficiency of an inhibitor to C1 esterase allows complement consumption to go unchecked so that vasoactive mediators are generated. To confirm the diagnosis, serum C1 esterase inhibitor level and C4 level should both be checked as the level of C1 esterase inhibitor is not always depressed (there is a type where the inhibitor is present but does not work).

**Investigations**

The investigations will depend upon the presentation and type of urticaria. Many of the physical urticarias can be reproduced by appropriate physical tests. It is important to remember that antihistamines should be stopped for at least 3 days before these are undertaken.

### Table 8.4 Some exogenous causes of urticaria.

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs, both topical and systemic</strong></td>
</tr>
<tr>
<td><strong>Foods and food additives</strong></td>
</tr>
<tr>
<td><strong>Bites</strong></td>
</tr>
<tr>
<td><strong>Inhalants</strong></td>
</tr>
<tr>
<td><strong>Pollens</strong></td>
</tr>
<tr>
<td><strong>Insect venoms</strong></td>
</tr>
<tr>
<td><strong>Animal dander</strong></td>
</tr>
</tbody>
</table>

Bruising in their wake. Some bullous diseases, such as dermatitis herpetiformis, bullous pemphigoid and pemphigoid gestationis, begin as urticarial papules or plaques, but later bullae make the diagnosis obvious. On the face, erysipelas can be distinguished from angioedema by its sharp margin, redder colour and accompanying pyrexia. Hereditary angioedema must be distinguished from the angioedema accompanying urticaria as their treatments are completely different.

**Fig. 8.7** A massive urticarial reaction to a wasp sting.
In some patients with acute or contact urticaria, allergy testing in the form of radioallergosorban
tests (RAST) or prick tests (Chapter 3), using only allergens suggested by the history, can sometimes be of help. Many patients with chronic urticaria are sure that their problems could be solved by intensive allergy tests, and ask repeatedly for them, but this is seldom worthwhile.

### Treatment

The ideal is to find a cause and then to eliminate it. In addition, aspirin—in any form—should be banned. The treatment for each type of urticaria is outlined in Table 8.5. In general, antihistamines are the mainstays of symptomatic treatment. Cetirizine 10 mg/day and loratadine 10 mg/day, both with half-lives of around 12 h, are useful. If necessary, these can be supplemented with shorter acting antihistamines, e.g. hydroxyzine 10–25 mg up to every 6 h (Formulary 2, p. 345) and acrivastine, 8 mg three times daily. Alternatively they can be combined with a longer acting antihistamine (such as chlorpheniramine maleate 12 mg sustained-release tablets every 12 h) so that peaks and troughs are blunted, and histamine activity is blocked throughout the night. If the eruption is not controlled, the dose of hydroxyzine can often be increased and still tolerated. H2-blocking antihistamines (e.g. cimetidine) may add a slight benefit if used in conjunction with an H1 histamine antagonist. Chlorpheniramine or diphenhydramine are often used during pregnancy because of their long record of safety, but cetirizine, loratidine and mizolastine should be avoided. Sympathomimetic agents can help urticaria, although the effects of adrenaline (epinephrine) are short lived. Pseudoephedrine (30 or 60 mg every 4 h) or terbutaline (2.5 mg every 8 h) can sometimes be useful adjuncts.

A tapering course of systemic corticosteroids may be used, but only when the cause is known and there are no contraindications, and certainly not as a panacea to control chronic urticaria or urticaria of unknown cause. For the treatment of anaphylaxis see p. 312.

### Table 8.5 Some types of urticaria and their management.

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold urticaria</td>
<td>Avoid cold</td>
</tr>
<tr>
<td></td>
<td>Protective clothing</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Avoid sun exposure</td>
</tr>
<tr>
<td></td>
<td>Protective clothing</td>
</tr>
<tr>
<td></td>
<td>Sunscreens and sun blocks</td>
</tr>
<tr>
<td></td>
<td>Beta-carotene</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>Avoid heat</td>
</tr>
<tr>
<td></td>
<td>Minimize anxiety</td>
</tr>
<tr>
<td></td>
<td>Avoid excessive exercise</td>
</tr>
<tr>
<td></td>
<td>Anticholinergics</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
</tr>
<tr>
<td></td>
<td>Tranquillizers</td>
</tr>
<tr>
<td>Dermographism</td>
<td>Avoid trauma</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
</tr>
<tr>
<td>Hereditary angioedema</td>
<td>Avoid trauma</td>
</tr>
<tr>
<td></td>
<td>Attenuated androgenic steroids as prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Tracheotomy may be necessary</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Remove cause</td>
</tr>
<tr>
<td>urticarias</td>
<td>Antihistamines (H1 + H2)</td>
</tr>
<tr>
<td></td>
<td>Sympathomimetics</td>
</tr>
<tr>
<td></td>
<td>Systemic steroids (rarely justified)</td>
</tr>
<tr>
<td></td>
<td>Avoid aspirin-containing drugs</td>
</tr>
</tbody>
</table>

### LEARNING POINTS

1. The treatment of choice is to find the cause and eliminate it.
2. You can learn more about the cause from the history than from tests.
3. Most patients with hives clear up quickly even if the cause is not obvious.
4. Use antihistamines in relatively high doses.
5. Avoid aspirins and systemic steroids in chronic urticaria.
6. Do not promise patients that all will be solved by allergy tests.
7. Take respiratory tract blockage seriously.

### Erythema multiforme

#### Cause

In erythema multiforme, the victim has usually reacted to an infection, often herpes simplex, or to a drug,
CHAPTER 8

Complications

There are usually no complications. However, severe lesions in the tracheo-bronchial tree of patients with Stevens–Johnson syndrome can lead to asphyxia, and ulcers of the bulbar conjunctiva to blindness. Corneal ulcers, anterior uveitis and panophthalmitis may also

but other factors have occasionally been implicated (Table 8.6).

Presentation

The symptoms of an upper respiratory tract infection may precede the eruption. Typically, annular non-scaling plaques appear on the palms, soles, forearms and legs. They may be slightly more purple than the wheals of ordinary urticaria. Individual lesions enlarge but clear centrally. A new lesion may begin at the same site as the original one, so that the two concentric plaques look like a target (Fig. 8.8). Some lesions blister. The Stevens–Johnson syndrome is a severe variant of erythema multiforme associated with fever and mucous membrane lesions. The oral mucosa, lips and bulbar conjunctivae are most commonly affected, but the nares, penis, vagina, pharynx, larynx and tracheo-bronchial tree may also be involved (Fig. 8.9).

Course

Crops of new lesions appear for 1 or 2 weeks, or until the responsible drug or other factor has been eliminated. Individual lesions last several days, and this differentiates them from the more fleeting lesions of an annular urticaria. The site of resolved lesions is marked transiently by hyperpigmentation, particularly in pigmented individuals. A recurrent variant of erythema multiforme exists, characterized by repeated attacks; this merges with a rare form in which lesions continue to develop over a prolonged period, even for years.

Complications

There are usually no complications. However, severe lesions in the tracheo-bronchial tree of patients with Stevens–Johnson syndrome can lead to asphyxia, and ulcers of the bulbar conjunctiva to blindness. Corneal ulcers, anterior uveitis and panophthalmitis may also

Table 8.6 Some causes of erythema multiforme.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infections, especially:</td>
<td>herpes simplex</td>
</tr>
<tr>
<td></td>
<td>hepatitis A, B and C</td>
</tr>
<tr>
<td></td>
<td>mycoplasma</td>
</tr>
<tr>
<td></td>
<td>orf</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td>coccidioidomycosis</td>
</tr>
<tr>
<td>Parasitic infestations</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Malignancy, or its treatment</td>
<td></td>
</tr>
<tr>
<td>with radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>


Fig. 8.8 Erythema multiforme: bullous and target lesions occurring in a favourite site.

Fig. 8.9 Stevens–Johnson type of erythema multiforme. The eyelids were also severely involved.
occur. Genital ulcers can cause urinary retention, and phimosis or vaginal stricture after they heal.

**Differential diagnosis**

Erythema multiforme can mimic the annular variant of urticaria as described above. However, target lesions are pathognomonic of erythema multiforme. Its acral distribution, the way individual lesions last for more than 24 h, their purple colour and the involvement of mucous membranes all help to identify erythema multiforme. Other bullous disorders may enter the differential diagnosis (Chapter 9).

**Investigations**

The histology of erythema multiforme is distinctive. Its main features are epidermal necrosis and dermal changes, consisting of endothelial swelling, a mixed lymphohistiocytic perivascular infiltrate and papillary dermal oedema. The abnormalities may be predominantly epidermal or dermal, or a combination of both; they probably depend on the age of the lesion biopsied.

Most investigations are directed towards identifying a cause. A careful history helps rule out a drug reaction. Tzanck smears (p. 35) or culture of suspicious prodromal vesicles may identify a precipitating herpes simplex infection, which usually is almost healed by the time the erythema multiforme erupts. A chest X-ray and serological tests should identify mycoplasmal pneumonia. A search for other infectious agents, neoplasia, endocrine causes or collagen disease is sometimes necessary, especially when the course is prolonged or recurrent. About 50% of cases have no demonstrable provoking factor.

**Treatment**

The best treatment for erythema multiforme is to identify and remove its cause. In mild cases, only symptomatic treatment is needed and this includes the use of antihistamines.

The Stevens–Johnson syndrome, on the other hand, may demand immediate consultation between dermatologists and specialists in other fields such as ophthalmology, urology and infectious diseases, depending on the particular case. Intravenous infusions of human gammaglobulin seem to be worthwhile. The use of systemic steroids to abort Stevens–Johnson syndrome is debatable, but many believe that a short course (e.g. prednisolone 80 mg/day in divided doses in an adult) helps. However, the dose should be tapered rapidly or stopped because prolonged treatment in the Stevens–Johnson syndrome has been linked, controversially, with a high complication rate. Good nursing care with attention to the mouth and eyes is essential. The prevention of secondary infection, maintenance of a patent airway, good nutrition, and proper fluid and electrolyte balance are important.

Herpes simplex infections should be suspected in recurrent or continuous erythema multiforme of otherwise unknown cause. Treatment with oral acyclovir 200 mg three to five times daily or valciclovir 500 mg twice daily (Formulary 2, p. 344) may prevent attacks, both of herpes simplex and of the recurrent erythema multiforme which follows it.

**Erythema nodosum**

Erythema nodosum is an inflammation of the subcutaneous fat (panniculitis). It is an immunological reaction, elicited by various bacterial, viral and fungal infections, malignant disorders, drugs and by a variety of other causes (Table 8.7).

**Presentation**

The characteristic lesion is a tender red nodule developing alone or in groups on the legs and forearms or, rarely, on other areas such as the thighs, face, breasts or other areas where there is fat (Fig. 8.10). Some patients also have painful joints and fever.
CHAPTER 8

Mycobacterium leprae. These patients have severe malaise, arthralgia and fever.

Differential diagnosis

The differential diagnosis of a single tender red nodule is extensive and includes trauma, infection (early cellulitis or abscess) and phlebitis.

When lesions are multiple or bilateral, infection becomes less likely unless the lesions are developing in a sporotrichoid manner (p. 200). Other causes of a nodular panniculitis, which may appear like erythema nodosum, include panniculitis from pancreatitis, cold, trauma, injection of drugs or other foreign substances, withdrawal from systemic steroids, lupus erythematosus, superficial migratory thrombophlebitis, polyarteritis nodosa and a deficiency of α1-antitrypsin. Some people use the term nodular vasculitis to describe a condition like erythema nodosum that lasts for more than 6 months.

Investigations

Erythema nodosum demands a careful history, physical examination, a chest X-ray, throat culture for streptococcus, a Mantoux test and an antistreptolysin-O (ASO) titre. If the results are normal, and there are no symptoms or physical findings to suggest other causes, extensive investigations can be deferred because the disease will usually resolve.

Treatment

The ideal treatment for erythema nodosum is to identify and eliminate its cause if possible. For example, if culture or an ASO test confirms a streptococcal infection, a suitable antibiotic should be recommended. Bed rest is also an important part of treatment. NSAIDs such as aspirin, indomethacin or ibuprofen may be helpful. Systemic steroids are usually not needed. For reasons that are not clear, potassium iodide in a dosage of 400–900 mg/day can help, but should not be used for longer than 6 months.

Complications

The nodules may be so tender that walking is difficult. Erythema nodosum leprosum occurs when lepromatous leprosy patients establish cell-mediated immunity to

Table 8.7 Some causes of erythema nodosum.

<table>
<thead>
<tr>
<th>Infections</th>
<th>Viruses</th>
<th>Fungi (especially coccidioidomycosis)</th>
<th>Drugs (e.g. sulphonamides, oral contraceptive agents)</th>
<th>Systemic disease (e.g. sarcoidosis, ulcerative colitis, Crohn’s disease, Behçet’s disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria (e.g. streptococci, tuberculosis, brucellosis, leprosy, yersinia)</td>
<td>Mycoplasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rickettsia</td>
<td>Chlamydia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Viruses</td>
<td>Fungi (especially coccidioidomycosis)</td>
<td>Drugs (e.g. sulphonamides, oral contraceptive agents)</td>
<td>Systemic disease (e.g. sarcoidosis, ulcerative colitis, Crohn’s disease, Behçet’s disease)</td>
</tr>
</tbody>
</table>

Fig. 8.10 Erythema nodosum: large painful dusky plaques on the shins. Always investigate this important reaction pattern (see text).

Course

Lesions usually resolve in 6–8 weeks. In the interim, lesions may enlarge and new ones may occur at other sites. Like other reactive erythemas, erythema nodosum may persist if its cause is not removed.

Vasculitis

Whereas the reactive erythemas are associated with some inflammation around superficial or deep blood
vessels, the term vasculitis is reserved for those showing inflammation within the vessel wall, with endothelial cell swelling, necrosis or fibrinoid change. The clinical manifestations depend upon the size of the blood vessel affected.

**Leucocytoclastic (small vessel) vasculitis**  
(Syn: allergic or hypersensitivity vasculitis, anaphylactoid purpura)

**Cause**

Immune complexes may lodge in the walls of blood vessels, activate complement and attract polymorphonuclear leucocytes (Fig. 8.11). Enzymes released from these can degrade the vessel wall. Antigens in these immune complexes include drugs, auto-antigens, and infectious agents such as bacteria.

**Presentation**

The most common presentation of vasculitis is painful palpable purpura (Fig. 8.12). Crops of lesions arise in dependent areas (the forearms and legs in ambulatory patients, or on the buttoks and flanks in bedridden ones; Fig. 8.13). Some have a small, livid or black
skin signs include angioedema. General features include malaise and arthralgia.

**Course**

The course of the vasculitis varies with its cause, its extent, the size of blood vessel affected, and the involvement of other organs.

**Complications**

Vasculitis may simply be cutaneous; alternatively, it may be systemic and then other organs will be damaged, including the kidney, central nervous system, gastrointestinal tract and lungs.

**Differential diagnosis**

Small vessel vasculitis has to be separated from other causes of purpura (p. 145) such as abnormalities of the clotting system and sepsis (with or without vasculitis). Vasculitic purpuras are raised (palpable). Occasionally, the vasculitis may look like urticaria if its purpuric element is not marked. Blanching such an urticarial papule with a glass slide may reveal subtle purpura.

**Investigations**

Investigations should be directed toward identifying the cause and detecting internal involvement. Questioning may indicate infections; myalgias, abdominal pain, claudication, mental confusion and mononeuritis may indicate systemic involvement. A physical examination, chest X-ray, ESR and biochemical tests monitoring the function of various organs are indicated. However, the most important test is urine analysis, checking for proteinuria and haematuria, because vasculitis can affect the kidney subtly and so lead to renal insufficiency.

Skin biopsy will confirm the diagnosis of small vessel vasculitis. The finding of circulating immune complexes, or a lowered level of total complement (CH50) or C4, will implicate immune complexes as its cause. Tests for hepatitis virus, cryoglobulins, rheumatoid factor and antinuclear antibodies may also be needed.

Direct immunofluorescence can be used to identify immune complexes in blood vessel walls, but is seldom performed because of false-positive and false-negative results, as inflammation may destroy the complexes in a true vasculitis and induce non-specific deposition in other diseases. Henoch–Schönlein vasculitis is confirmed if IgA deposits are found in the blood vessels of a patient with the clinical triad of palpable purpura, arthritis and abdominal pain.

**Treatment**

The treatment of choice is to identify the cause and eliminate it. In addition, antihistamines and bed rest sometimes help. Colchicine 0.6 mg twice daily or dapsone 100 mg daily may be worth a trial, but require monitoring for side-effects (Formulary 2, p. 352). Patients whose vasculitis is damaging the kidneys or other internal organs may require systemic corticosteroids or immunosuppressive agents such as cyclophosphamide.

**Polyarteritis nodosa**

**Cause**

This necrotizing vasculitis of large arteries causes skin nodules, infarctive ulcers and peripheral gangrene.
Immune complexes may initiate this vasculitis, and sometimes contain hepatitis B or C virus or antigen. Other known causes are adulterated drugs, B-cell lymphomas and immunotherapy.

**Presentation**

Tender subcutaneous nodules appear along the line of arteries. The skin over them may ulcerate or develop stellate patches of purpura and necrosis. Splinter haemorrhages and a peculiar net-like vascular pattern (livedo reticularis) aid the clinical diagnosis. The disorder may be of the skin only (cutaneous polyarteritis nodosa), or also affect the kidneys, heart muscle, nerves and joints (Fig. 8.15). Patients may be febrile, lose weight and feel pain in the muscles, joints or abdomen. Some develop peripheral neuropathy, hypertension and ischaemic heart disease. Renal involvement, with or without hypertension, is common.

**Course**

Untreated, systemic polyarteritis nodosa becomes chronic. Death, often from renal disease, is common, even in treated patients.
Differential diagnosis

Emboli, panniculitis and infarctions can cause a similar clinical picture. Wegener’s granulomatosis, allergic granulomatosis, temporal arteritis, and the vasculitis that accompanies systemic lupus erythematosus and rheumatoid arthritis should be considered.

Investigations

The laboratory findings are non-specific. An elevated ESR, neutrophil count, and gammaglobulin level are common. Investigations for cryoglobulins, rheumatoid factor, antinuclear antibody, antineutrophil antibodies and hepatitis C and B surface antigen are worthwhile, as are checks for disease in the kidneys, heart, liver and gut. Low levels of complement suggest active disease. The use of biopsy to confirm the diagnosis of large vessel vasculitis is not always easy as the arterial involvement may be segmental, and surgery itself difficult. Histological confirmation is most likely when biopsies are from a fresh lesion. Affected vessels show aneurysmal dilatation or necrosis, fibrinoid changes in their walls, and an intense neutrophilic infiltrate around and even in the vessel wall.

Treatment

Systemic steroids and cyclophosphamide improve chances of survival. Low-dose systemic steroids alone are usually sufficient for the purely cutaneous form.

Wegener’s granulomatosis

In this granulomatous vasculitis of unknown cause, fever, weight loss and fatigue accompany nasoro-pharyngeal symptoms such as rhinitis, hearing loss or sinusitis. Only half of the patients have skin lesions, usually symmetrical ulcers or papules on the extremities. Other organs can be affected, including the eye, joints, heart, nerves, lung and kidney. Antineutrophil antibodies are present in most cases and are a useful but non-specific diagnostic marker. Cyclophosphamide is the treatment of choice, used alone or with systemic steroids.

Further reading


Bullous diseases

Blisters are accumulations of fluid within or under the epidermis. They have many causes, and a correct clinical diagnosis must be based on a close study of the physical signs.

The appearance of a blister is determined by the level at which it forms. Subepidermal blisters occur between the dermis and the epidermis. Their roofs are relatively thick and so they tend to be tense and intact. They may contain blood. Intraepidermal blisters appear within the prickle cell layer of the epidermis, and so have thin roofs and rupture easily to leave an oozing denuded surface: this tendency is even more marked with subcorneal blisters, which form just beneath the stratum corneum at the outermost edge of the viable epidermis, and therefore have even thinner roofs.

Sometimes the morphology or distribution of a bullous eruption gives the diagnosis away, as in herpes simplex or zoster. Sometimes the history helps too, as in cold or thermal injury, or in an acute contact dermatitis. When the cause is not obvious, a biopsy should be taken to show the level in the skin at which the blister has arisen. A list of differential diagnoses, based on the level at which blisters form, is given in Fig. 9.1.

The bulk of this chapter is taken up by the three most important immunobullous disorders—pemphigus, pemphigoid and dermatitis herpetiformis (Table 9.1) —and by the group of inherited bullous disorders known as epidermolysis bullosa. Our understanding of both groups has advanced in parallel, as several of the skin components targeted by autoantibodies in the immunobullous disorders are the same as those inherited in an abnormal form in epidermolysis bullosa.

**Bullous disorders of immunological origin**

In pemphigus and pemphigoid, the damage is done by autoantibodies directed at molecules that normally bind the skin (p. 11 and p. 15). This type of mechanism has not yet been proven for dermatitis herpetiformis; but the characteristic deposition of immunoglobulin (Ig) A in the papillary dermis, and an association with a variety of autoimmune disorders, both suggest an immunological basis for the disease.

**Fig. 9.1** The differential diagnosis of bullous diseases based on the histological location of the blister.
Chapter 9

Presentation

Pemphigus vulgaris is characterized by flaccid blisters of the skin (Fig. 9.2) and mouth (Fig. 9.3) and, after the blisters rupture, by widespread painful erosions. Most patients develop the mouth lesions first. Shearing pemphigus is severe and potentially life-threatening. There are two main types. The most common is pemphigus vulgaris, which accounts for at least three-quarters of all cases, and for most of the deaths. Pemphigus vegetans is a rare variant of pemphigus vulgaris. The other important type of pemphigus, superficial pemphigus, also has two variants: the generalized foliaceus type and localized erythematous type. A few drugs, led by penicillamine, can trigger a pemphigus-like reaction, but autoantibodies are then seldom found. Finally, a rare type of pemphigus (paraneoplastic pemphigus) has been described in association with a thymoma or an underlying carcinoma; it is characterized by unusually severe mucosal lesions.

Cause

All types of pemphigus are autoimmune diseases in which pathogenic IgG antibodies bind to antigens within the epidermis. The main antigens are desmoglein 3 (in pemphigus vulgaris) and desmoglein 1 (in superficial pemphigus). Both are cell-adhesion molecules of the cadherin family (see Table 2.5), found in desmosomes. The antigen–antibody reaction interferes with adhesion, causing the keratinocytes to fall apart.

Table 9.1 Distinguishing features of the three main immunobullous diseases.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Site of blisters</th>
<th>General health</th>
<th>Blisters in mouth</th>
<th>Nature of blisters</th>
<th>Circulating antibodies</th>
<th>Fixed antibodies</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus</td>
<td>Middle age</td>
<td>Trunk, flexures and scalp</td>
<td>Poor</td>
<td>Common</td>
<td>Superficial and flaccid</td>
<td>IgG to intercellular adhesion proteins</td>
<td>IgG in intercellular space</td>
<td>Steroids, Immunosuppressives</td>
</tr>
<tr>
<td>Pemphigoid</td>
<td>Old</td>
<td>Often flexural</td>
<td>Good</td>
<td>Rare</td>
<td>Tense and blood-filled</td>
<td>IgG to basement membrane region</td>
<td>IgG at basement membrane</td>
<td>Steroids, Immunosuppressives</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Primarily adults</td>
<td>Elbows, knees, upper back, buttocks</td>
<td>Itchy</td>
<td>Rare</td>
<td>Small, excoriated and grouped</td>
<td>IgG to the endomysium of muscle</td>
<td>IgA granular deposits in papillary dermis</td>
<td>Gluten-free diet, Dapsone, Sulphapyridine</td>
</tr>
</tbody>
</table>

Pemphigus

Pemphigus is severe and potentially life-threatening. There are two main types. The most common is pemphigus vulgaris, which accounts for at least three-quarters of all cases, and for most of the deaths. Pemphigus vegetans is a rare variant of pemphigus vulgaris. The other important type of pemphigus, superficial pemphigus, also has two variants: the generalized foliaceus type and localized erythematous type. A few drugs, led by penicillamine, can trigger a pemphigus-like reaction, but autoantibodies are then seldom found. Finally, a rare type of pemphigus (paraneoplastic pemphigus) has been described in association with a thymoma or an underlying carcinoma; it is characterized by unusually severe mucosal lesions.

Fig. 9.2 Pemphigus vulgaris: widespread erosions that have followed blisters.

Presentation

Pemphigus vulgaris is characterized by flaccid blisters of the skin (Fig. 9.2) and mouth (Fig. 9.3) and, after the blisters rupture, by widespread painful erosions. Most patients develop the mouth lesions first. Shearing
Course
The course of all forms of pemphigus is prolonged, even with treatment, and the mortality rate of pemphigus vulgaris is still at least 15%. Superficial pemphigus is less severe. With modern treatments, most patients with pemphigus can live relatively normal lives, with occasional exacerbations.

Complications
Complications are inevitable with the high doses of steroids and immunosuppressive drugs that are needed to control the condition. Indeed, side-effects of treatment are now the leading cause of death. Infections of all types are common. The large areas of denudation may become infected and smelly, and severe oral ulcers make eating painful.

Differential diagnosis
Widespread erosions may suggest a pyoderma, impetigo, epidermolysis bullosa or ecthyma. Mouth ulcers can be mistaken for aphthae, Behçet’s disease or a herpes simplex infection.

Investigations
Biopsy shows that the vesicles are intraepidermal, with rounded keratinocytes floating freely within the blister cavity (acantholysis). Direct immunofluorescence (p. 39) of adjacent normal skin shows intercellular epidermal deposits of IgG and C3 (Fig. 9.5). The serum from a patient with pemphigus contains antibodies that bind to the desmogleins in the desmosomes of normal epidermis, so that indirect immunofluorescence (p. 39) can also be used to confirm the diagnosis. The titre of these antibodies correlates loosely with clinical activity and may guide changes in the dosage of systemic steroids.

LEARNING POINT
Pemphigus is more attacking than pemphigoid and needs higher doses of steroids to control it.
grouped or located in body folds. Bullous impetigo is caused by *Staphylococcus aureus*.

**Scalded skin syndrome** (p. 192)

A toxin elaborated by some strains of *S. aureus* makes the skin painful and red; later it peels like a scald. The staphylococcus is usually hidden (e.g. conjunctiva, throat, wound, furuncle).

**Miliaria crystallina** (p. 161)

Here sweat accumulates under the stratum corneum leading to the development of multitudes of uniformly spaced vesicles without underlying redness. Often this occurs after a fever or heavy exertion. The vesicles look like droplets of water lying on the surface, but the skin is dry to the touch. The disorder is self-limiting and needs no treatment.

**Subcorneal pustular dermatosis**

As its name implies, the lesions are small groups of pustules rather than vesicles. However, the pustules pout out of the skin in a way that suggests they were once vesicles (like the vesico-pustules of chickenpox).
The cause of this rare disease is unknown, but oral dapsone (Formulary 2, p. 351) usually suppresses it.

**Acute dermatitis** (Chapter 7)

Severe acute eczema, especially of the contact allergic type, can be bullous. Plants such as poison ivy, poison oak or primula are common causes. The varied size of the vesicles, their close grouping, their asymmetry, their odd configurations (e.g. linear, square, rectilinear) and a history of contact with plants are helpful guides to the diagnosis.

**Pompholyx** (p. 89)

In pompholyx, highly itchy small eczematous vesicles occur along the sides of the fingers, and sometimes also on the palms and soles. Some call it ‘dyshidrotic eczema’, but the vesicles are not related to sweating or sweat ducts. The disorder is very common, but its cause is not known.

**Viral infections** (Chapter 14)

Some viruses create blisters in the skin by destroying epithelial cells. The vesicles of herpes simplex and zoster are the most common examples.

**Transient acantholytic dermatosis** *(Grover’s disease)*

Itchy vesicles appear on the sun-damaged skin of the trunk, usually of middle-aged males. The cause is not known and the condition can be persistent—despite its name.

**Subepidermal immunobullous disorders**

These can be hard to separate on clinical grounds and only the two most important, pemphigoid and dermatitis herpetiformis, are described in detail here. Several others are mentioned briefly.

**Pemphigoid**

Pemphigoid is an autoimmune disease. Serum from about 70% of patients contains antibodies that bind *in vitro* to normal skin at the basement membrane zone. However, their titre does not correlate with clinical disease activity. The IgG antibodies bind to two main antigens: most commonly to BP230 (within the cellular part of the hemidesmosome, p. 15), and less often to BP180 (a transmembrane molecule with one end within the hemidesmosome and the other bound to the lamina lucida). Complement is then activated (p. 24), an inflammatory cascade starts and mast cells degranulate, liberating a variety of inflammatory mediators.

**Presentation**

Pemphigoid is a chronic, usually itchy, blistering disease, mainly affecting the elderly. The tense bullae can arise from normal skin but usually do so from urticarial plaques (Fig. 9.6). The flexures are often affected; the mucous membranes usually are not. The Nikolsky test is negative.

**Course**

Pemphigoid is usually self-limiting and treatment can often be stopped after 1–2 years.
Complications

Untreated, the disease causes much discomfort and loss of fluid from ruptured bullae. Systemic steroids and immunosuppressive agents carry their usual complications if used long-term (Formulary 2, p. 348 and p. 346, respectively). The validity of a possible association with internal malignancy is still debated.

Differential diagnosis

Pemphigoid may look like other bullous diseases, especially epidermolysis bullosa acquisita, bullous lupus erythematosus, dermatitis herpetiformis, pemphigoid gestationis, bullous erythema multiforme and linear IgA bullous disease. Immunofluorescence helps to separate it from these (Fig. 9.5).

Investigations

The histology is that of a subepidermal blister, often filled with eosinophils. Direct immunofluorescence shows a linear band of IgG and C3 along the basement membrane zone. Indirect immunofluorescence, using serum from the patient, identifies IgG antibodies that react with the basement membrane zone in some 70% of patients (Fig. 9.7).

Treatment

In the acute phase, prednisolone or prednisone (Formulary 2, p. 348) at a dosage of 40–60 mg/day is usually needed to control the eruption. Immunosuppressive agents may also be required. The dosage is reduced as soon as possible, and patients end up on a low maintenance regimen of systemic steroids, taken on alternate days until treatment is stopped. For unknown reasons, tetracyclines and niacinamide help some patients.

Pemphigoid gestationis (herpes gestationis)

This is pemphigoid occurring in pregnancy, or in the presence of a hydatidiform mole or a choriocarcinoma. As in pemphigoid, most patients have linear deposits of C3 along the basement membrane zone (Fig. 9.5), although IgG is detected less often. The condition usually remits after the birth but may return in future pregnancies. It is not caused by a herpes virus: the name herpes gestationis should be discarded now so that the disease is not confused with herpes genitalis. Treatment is with systemic steroids. Oral contraceptives should be avoided.

Cicatricial pemphigoid (Fig. 9.8)

Like pemphigoid itself, cicatricial pemphigoid is an autoimmune skin disease showing IgG and C3 deposition at the basement membrane zone (Fig. 9.5). The antigens are often as in pemphigoid, but other antigens are sometimes targeted such as laminin 5 (in anchoring filaments). The condition differs from pemphigoid in that its blisters and ulcers occur mainly on mucous membranes such as the conjunctivae, the mouth and genital tract. Bullae on the skin itself are uncommon. Lesions heal with scarring: around the eyes this may cause blindness, especially when the palpebral conjunctivae are affected (Fig. 9.8). The condition tends to persist and treatment is relatively ineffective, although very potent local steroids, systemic steroids and immunosuppressive agents are

LEARNING POINTS

1. Death is uncommon and the disease is self-limiting.
2. Some elderly people get fatal side-effects from their systemic steroids. Reduce the dosage as soon as possible.
Dermatitis herpetiformis

Dermatitis herpetiformis is a very itchy chronic subepidermal vesicular disease, in which the vesicles erupt in groups as in herpes simplex—hence the name ‘herpetiformis’.

Cause

Gluten-sensitive enteropathy, demonstrable by small bowel biopsy, is always present, but most patients do not suffer from diarrhoea, constipation or malnutrition as the enteropathy is mild, patchy and involves only the proximal small intestine. Absorption of gluten, or another dietary antigen, may form circulating immune complexes that lodge in the skin. A range of antibodies can be detected, notably directed against reticulin, gliadin and endomysium—a component of smooth muscle. Granular deposits of IgA and C3 in the superficial dermis under the basement membrane zone (Fig. 9.5) induce inflammation, which then separates the epidermis from the dermis. These deposits clear slowly after the introduction of a gluten-free diet.

Presentation

The extremely itchy, grouped vesicles (Fig. 9.9) and urticated papules develop particularly over the elbows (Fig. 9.10) and knees, buttocks and shoulders. They are often broken by scratching before they reach any size. A typical patient therefore shows only grouped excoriations, sometimes with eczema-like changes added by scratching.

Course

The condition typically lasts for decades.

Complications

The complications of gluten-sensitive enteropathy include diarrhoea, abdominal pain, anaemia and, rarely, malabsorption. Small bowel lymphomas have been reported, and the use of a gluten-free diet may reduce this risk. There is a proven association with other autoimmune diseases, most commonly of the thyroid. Treatment, notably with dapsone (Formulary 2, p. 352), can cause side-effects.
IgA deposits remain in the skin, and the skin disease can drag on for many months. Because of this, and because a gluten-free diet is hard to follow and enjoy, some patients prefer to combine the diet with dapsone (Formulary 2, p. 352) or sulphapyridine (sulfapyridine) at the start, although both can cause severe rashes, haemolytic anaemia (especially in those with glucose-6-phosphate dehydrogenase deficiency), leucopenia, thrombocytopenia, methaemoglobinaemia and peri-

Differential diagnosis

The disorder masquerades as scabies, an excoriated eczema, insect bites or neurodermatitis.

Investigations

If a vesicle can be biopsied before it is scratched away, the histology will be that of a subepidermal blister, with neutrophils packing the adjacent dermal papillae. Direct immunofluorescence of uninvolved skin shows granular deposits of IgA, and usually C3, in the dermal papillae and superficial dermis (Fig. 9.5). Small bowel biopsy is no longer recommended as routine because the changes are often patchy. Tests for malabsorption are seldom needed.

Treatment

The disorder responds to a gluten-free diet, which should be supervised by a dietitian. Adherence to this can be monitored using the titre of antiendomysial antibody, which should fall if gluten is strictly avoided. The bowel changes revert quickly to normal but

**LEARNING POINTS**

1. Biopsy non-involved skin to demonstrate the diagnostic granular deposits of IgA in the dermal papillae.
2. The gluten enteropathy of dermatitis herpetiformis seldom causes frank malabsorption.
3. Dapsone works quickly and a gluten-free diet only very slowly. Combine the two at the start and slowly reduce the dapsone.
Bullous diseases

Other causes of subepidermal blisters

Porphyria cutanea tarda (p. 287)
The bullae and erosions occur on the backs of the hands and on other areas exposed to sunlight.

Blisters in diabetes and renal disease
A few diabetics develop unexplained blisters on their legs or feet. The backs of the hands of patients with chronic renal failure may show changes rather like those of porphyria cutanea tarda (pseudoporphyria). Frusemide (furosemide) can contribute to blister formation.

Bullous lupus erythematosus
Vesicles and bullae may be seen in severe active systemic lupus erythematosus (p. 119). This disorder is uncommon and carries a high risk of kidney disease. Non-cutaneous manifestations of systemic lupus erythematosus do not respond to dapsone; however, the bullae do.

Bullous erythema multiforme
Bullous erythema multiforme in the form of the Stevens–Johnson syndrome is discussed in Chapter 8.

Toxic epidermal necrolysis (Lyell’s disease)
Cause
Toxic epidermal necrolysis is usually a drug reaction, most commonly to sulphonamides, barbiturates, carbamazepine or allopurinol (Chapter 22), but can also be a manifestation of graft-vs.-host disease. Sometimes it is unexplained.

Presentation
The skin becomes red and intensely painful, and then begins to come off in sheets like a scald. This leaves an eroded painful glistening surface (Fig. 9.11). Nikolsky’s sign is positive (p. 109). The mucous membranes may be affected, including the mouth, eyes, and even the bronchial tree.

Course
The condition usually clears if the offending drug is stopped. New epidermis grows out from hair follicles so that skin grafts are not usually needed. The disorder may come back if the drug is taken again.

Complications
Toxic epidermal necrolysis is a skin emergency and can be fatal. Infection, and the loss of fluids and electrolytes, are life-threatening, and the painful denuded skin surfaces make life a misery. Corneal scarring may remain when the acute episode has settled.

Differential diagnosis
The epidermolysis of the staphylococcal scalded skin syndrome (p. 192) looks like toxic epidermal necrolysis clinically, but only the stratum corneum is lost. Whereas toxic epidermal necrolysis affects adults, the staphylococcal scalded skin syndrome is seen in infancy or early childhood. Histology differentiates the two. Pemphigus may also look similar, but starts more slowly and is more localized. Severe graft-vs.-host reactions can also cause this syndrome. Some believe that toxic epidermal necrolysis can evolve from Stevens–Johnson syndrome because some patients have the clinical features of both.
Investigations

Biopsy helps to confirm the diagnosis. The split is subepidermal in toxic epidermal necrolysis, and the entire epidermis may be necrotic. A frozen section provides a quick answer if there is genuine difficulty in separating toxic epidermal necrolysis from the scalded skin syndrome (p. 192). There are no tests to tell which drug, if any, caused the disease.

Treatment

If toxic epidermal necrolysis is caused by a drug, this must be stopped (Chapter 22); otherwise, treatment relies mainly on symptomatic management. Intensive nursing care and medical support are needed, including the use of central venous lines, intravenous fluids and electrolytes. Many patients are treated in units designed to deal with extensive thermal burns. Air suspension beds increase comfort. The weight of opinion has turned against the use of systemic corticosteroids but, if they are given, it should be for short periods only, right at the start. Intravenous IgG seems more promising.

Epidermolysis bullosa

There are many types of epidermolysis bullosa: the five main ones are listed in Table 9.2. All are characterized by an inherited tendency to develop blisters after minimal trauma, although at different levels in the skin (Fig. 9.12). The more severe types have a catastrophic impact on the lives of sufferers. Acquired epidermolysis bullosa is not inherited and was discussed earlier in this chapter.

Table 9.2 Simplified classification of epidermolysis bullosa.

<table>
<thead>
<tr>
<th>Type</th>
<th>Mode of inheritance</th>
<th>Level of split</th>
<th>Mutations in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple epidermolysis bullosa</td>
<td>Usually autosomal dominant</td>
<td>Intraepidermal</td>
<td>Keratins 5 and 14</td>
</tr>
<tr>
<td>Junctional epidermolysis bullosa (epidermolysis bullosa letalis)</td>
<td>Autosomal recessive</td>
<td>Lamina lucida</td>
<td>Components of the hemidesmosome-anchoring filaments (e.g. laminins, integrins and bullos pemphigoid 180 molecule)</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>Autosomal dominant</td>
<td>Beneath lamina densa</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>Autosomal recessive</td>
<td>Beneath lamina densa</td>
<td>Type VII collagen</td>
</tr>
<tr>
<td>Acquired epidermolysis bullosa</td>
<td>Not inherited</td>
<td>Dermal side of lamina densa</td>
<td>Nil</td>
</tr>
</tbody>
</table>
Autosomal dominant dystrophic epidermolysis bullosa

In this type blisters appear in late infancy. They are most common on friction sites (e.g. the knees, elbows and fingers), healing with scarring and milia formation. The nails may be deformed or even lost. The mouth is not affected. The only treatment is to avoid trauma and to dress the blistered areas.

Autosomal recessive dystrophic epidermolysis bullosa

In this tragic form of epidermolysis bullosa, blisters start in infancy. They are most common on friction sites (e.g. the knees, elbows and fingers), healing with scarring and milia formation. The nails may be deformed or even lost. The mouth is not affected. The only treatment is to avoid trauma and to dress the blistered areas.

Junctional epidermolysis bullosa

The abnormalities in the basal lamina include loss of anchoring filaments and defective laminins (p. 15; see Fig. 2.9). This rare and often lethal condition is evident at birth. The newborn child has large raw areas and flaccid blisters, which are slow to heal (Fig. 9.13). The peri-oral and peri-anal skin is usually involved, as are the nails and oral mucous membrane. There is no effective systemic treatment. Hopes for the future include adding the normal gene to epidermal stem cells, and then layering these onto the denuded skin.

Dystrophic epidermolysis bullosa

There are many subtypes, all of which probably result from abnormalities of collagen VII, the major structural component of anchoring fibrils.
Further reading


The cardinal feature of these conditions is inflammation in the connective tissue which leads to dermal atrophy or sclerosis, to arthritis, and sometimes to abnormalities in other organs. In addition, antibodies form against normal tissues and cellular components; these disorders are therefore classed as autoimmune.

Many have difficulty in remembering which antibody features in which condition: Table 10.1 should help here.

The main connective tissue disorders present as a spectrum ranging from the benign cutaneous variants to severe multisystem diseases (Table 10.2).

Lupus erythematosus

Lupus erythematosus (LE) is a good example of such a spectrum, ranging from the purely cutaneous type (discoid LE), through patterns associated with some internal problems (disseminated discoid LE and subacute cutaneous LE), to a severe multisystem disease (systemic lupus erythematosus, SLE; Table 10.2).

Systemic lupus erythematosus

Cause

This is unknown, but hereditary factors, e.g. complement deficiency and certain HLA types, increase susceptibility. Particles looking like viruses have been seen in endothelial cells, and in other tissues, but their role is not clear. Patients with LE have autoantibodies to DNA, nuclear proteins and to other normal antigens, and this points to an autoimmune cause. Exposure to sunlight and artificial ultraviolet radiation (UVR), pregnancy and infection may precipitate the disease or lead to flare-ups. Some drugs, such as hydralazine and procainamide trigger SLE in a dose-dependent way, whereas others including oral contraceptives, anticonvulsants, minocycline and captopril, precipitate the disease just occasionally.

Presentation

Typically, but not always, the onset is acute. SLE is an uncommon disorder, affecting women more often than men (in a ratio of about 8 : 1). The classic rash of acute SLE is an erythema of the cheeks and nose in the rough shape of a butterfly (Figs 10.1 and 10.2), with facial swelling. Occasionally, a few blisters may be seen. Some patients develop widespread discoid papulosquamous plaques very like those of discoid LE; others, about 20% of patients, have no skin disease at any stage.

Other dermatological features include peri-ungual telangiectasia (see Fig. 10.7), erythema over the digits, hair fall (especially at the frontal margin of the scalp), and photosensitivity. Ulcers may occur on the palate, tongue or buccal mucosa.

Course

The skin changes may be transient, continuous or recurrent; they correlate well with the activity of the systemic disease. Acute SLE may be associated with fever, arthritis, nephritis, polyarteritis, pleurisy, pneumonia, pericarditis, myocarditis and involvement of the central nervous system. Internal involvement can be fatal, but the overall prognosis now is for about three-quarters of patients to survive for 15 years. Renal involvement suggests a poorer prognosis.

Complications

The skin disease may cause scarring or hyperpigmentation, but the main dangers lie with damage to other
Table 10.1 Some important associations with non-organ-specific autoantibodies.

<table>
<thead>
<tr>
<th>Antibody directed against</th>
<th>Nucleoprotein (ANA or ANF)* (IF pattern in brackets)</th>
<th>Double stranded DNA</th>
<th>Ro (SSA) and La (SSB)</th>
<th>Sm (ENA)</th>
<th>Cardiolipin</th>
<th>Nuclear RNP</th>
<th>Centromere</th>
<th>Histones</th>
<th>Jo-1</th>
<th>Topoisomerase (Scl-70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discoid LE</td>
<td>+ive in up to 35% (homogenous and speckled)</td>
<td>Rarely +ive</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Subacute LE</td>
<td>+ive in up to 80% (homogenous and speckled)</td>
<td>+ive in 60%</td>
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<td></td>
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<td></td>
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<tr>
<td>Systemic LE</td>
<td>+ive in up to 100% (homogenous and speckled)</td>
<td>+ive in 50–70% (esp with nephritis)</td>
<td>+ive in 30%</td>
<td>+ive in subset with recurrent abortions, thrombosis, livedo and skin necrosis</td>
<td>+ive in 6%</td>
<td>+ive in drug-induced cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dermatomyositis</td>
<td>+ive in up to 80% (speckled)</td>
<td>Occasionally +ive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systemic sclerosis</td>
<td>+ive in up to 90% (speckled and nucleolar)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed connective tissue disorder</td>
<td>+ive in 100% (speckled)</td>
<td>+ive in high titre—up to 100%</td>
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* Antibodies tested against human substrates (e.g. Human Hep. 2 cells).
Connective tissue disorders involve the failure of organs and the side-effects of treatment, especially systemic steroids.

**Differential diagnosis**

SLE is a great imitator. Its malar rash can be confused with sunburn, polymorphic light eruption (p. 238) and rosacea (p. 156). The discoid lesions are distinctive, but are also seen in discoid LE and in subacute cutaneous LE. Occasionally, they look like psoriasis or lichen planus (p. 64). The hair fall suggests telogen effluvium (p. 168). Plaques on the scalp may cause a scarring alopecia. SLE should be suspected when a characteristic rash is combined with fever, malaise and internal disease (Table 10.3).

**Investigations**

Conduct a full physical examination, looking for internal disease. Biopsy of skin lesions is worthwhile because the pathology and immunopathology are distinctive. There is usually some thinning of the epidermis,
other drugs (e.g. antihypertensive therapy or anticonvulsants) may also be needed. Antimalarial drugs may help some patients with marked photosensitivity, as may sunscreens. Intermittent intravenous infusions of gamma globulin show promise. Long-term and regular follow-up is necessary.

Subacute cutaneous lupus erythematosus

This is less severe than acute SLE, but is also often associated with systemic disease. Its cause is unknown, but probably involves an antibody-dependent cellular cytotoxic attack on basal cells by K cells bridged by antibody to Ro (SS-A) antigen.

Presentation

Patients with subacute cutaneous LE are often photosensitive. The skin lesions are sharply margined

Table 10.4 Investigations in SLE.

<table>
<thead>
<tr>
<th>Test</th>
<th>Usual findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin biopsy</td>
<td>Degeneration of basal cells, epidermal thinning, inflammation around appendages</td>
</tr>
<tr>
<td>Skin immunofluorescence</td>
<td>Fibrillar or granular deposits of IgG, IgM, IgA and/or C3 alone in basement membrane zone</td>
</tr>
<tr>
<td>Haematology</td>
<td>Anaemia, raised ESR, thrombocytopenia, decreased white cell count</td>
</tr>
<tr>
<td>Immunology</td>
<td>Antinuclear antibody, antibodies to double-stranded DNA, false positive tests for syphilis, low total complement level, lupus anticoagulant factor</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>Proteinuria or haematuria, often with casts if kidneys involved</td>
</tr>
<tr>
<td>Tests for function of other organs</td>
<td>As indicated by history but always test kidney and liver function</td>
</tr>
</tbody>
</table>
scaling psoriasiform plaques, sometimes annular, lying on the forehead, nose, cheeks, chest, hands and extensor surfaces of the arms. They tend to be symmetrical and are hard to tell from discoid LE, or SLE with widespread discoid lesions.

Course
As in SLE, the course is prolonged. The skin lesions are slow to clear but, in contrast to discoid LE, do so with little or no scarring.

Complications
Systemic disease is frequent, but not usually serious. Children born to mothers who have, or have had, this condition are liable to neonatal LE with transient annular skin lesions and permanent heart block.

Differential diagnosis
The morphology is characteristic, but lesions can be mistaken for psoriasis or widespread discoid LE. Annular lesions may resemble tinea corporis (p. 216) or figurate erythemas (p. 133).

Investigations
Patients with subacute cutaneous LE should be evaluated in the same way as those with acute SLE, although deposits of immunoglobulins in the skin and antinuclear antibodies in serum are present less often. Many have antibodies to the cytoplasmic antigen Ro (SS-A).

Treatment
Subacute cutaneous LE does better with antimalarials, such as hydroxychloroquine (Formulary 2, p. 352), than acute SLE. Oral retinoids (Formulary 2, p. 349) are also effective in some cases. Systemic steroids may be needed too.

Discoid lupus erythematosus
This is the most common form of LE. Patients with discoid LE may have one or two plaques only, or many in several areas. The cause is also unknown but UVR is one factor.

Fig. 10.3 Red scaly fixed plaques of discoid LE. This degree of scaling is not uncommon in the active stage. Follicular plugging is seen on the nose.

Presentation
Plaques show erythema, scaling, follicular plugging (like a nutmeg grater), scarring and atrophy, telangiectasia, hypopigmentation and a peripheral zone of hyperpigmentation. They are well demarcated and lie mostly on sun-exposed skin of the scalp, face and ears (Figs 10.1 and 10.3). In one variant (chilblain LE) dusky lesions appear on the fingers and toes.

Course
The disease may spread relentlessly, but in about half of the cases the disease goes into remission over the course of several years. Scarring is common and hair may be lost permanently if there is scarring in the scalp (Fig. 10.4). Whiteness remains after the inflammation has cleared, and hypopigmentation is common in dark-skinned people. Discoid LE rarely progresses to SLE.

Differential diagnosis
Psoriasis is hard to tell from discoid LE when its plaques first arise but has larger thicker scales, and later it is usually symmetrical and affects sites different from
those of discoid LE. Discoid LE is more common on the face and ears, and in sun-exposed areas, whereas psoriasis favours the elbows, knees, scalp and sacrum. Discoid LE is far more prone than psoriasis to scar and cause hair loss. Jessner’s lymphocytic infiltration is best viewed as a dermal form of discoid LE.

Investigations
Most patients with discoid LE remain well. However, screening for SLE and internal disease is still worthwhile. A skin biopsy is most helpful if taken from an untreated plaque where appendages are still present (Fig. 10.5). Direct immunofluorescence shows deposits of IgG, IgM, IgA and C3 at the basement membrane zone. Biopsies for direct immunofluorescence are best taken from older untreated plaques. Blood tests are usually normal but occasionally serum contains antinuclear antibodies (Table 10.5).

Treatment
Discoid LE needs potent or very potent topical corticosteroids (Formulary 1, p. 333). In this condition, it is justifiable to use them on the face, as the risk of scarring is worse than that of atrophy. Topical steroids should be applied twice daily until the lesions disappear or side-effects, such as atrophy, develop; weaker preparations can then be used for maintenance. If discoid LE does not respond to this, intrallesional injections of triamcinolone (2.5 or 10 mg/mL) may help. Stubborn and widespread lesions often do well with oral antimalarials such as hydroxychloroquine (Formulary 2, p. 352), but rarely these cause irreversible eye damage. The eyes should therefore be tested before and at intervals during treatment. Sun avoidance and screens are also important. Oral retinoids (Formulary 2, p. 349) and thalidomide have proved helpful in stubborn cases but a specialist, with experience of their use, should prescribe these controlled treatments and supervise management.
Dermatomyositis

Dermatomyositis is a subset of polymyositis with distinctive skin changes. There are adult and juvenile types (Table 10.2). The cause is unknown but an autoimmune mechanism seems likely. Autoantibodies to striated muscle are found. When starting after the age of 40, dermatomyositis may signal an internal malignancy. Presumably, the epitopes of some tumour antigens are so similar to those of muscle antigens that antibodies directed against the tumour cross-react with muscle cells and initiate the disease in a few adults with internal malignancy. Serological evidence for acute toxoplasmosis in polymyositis-dermatomyositis was found in one series.

Presentation

The skin signs are characteristic. Typical patients have a faint lilac discoloration around their eyes (sometimes called ‘heliotrope’ because of the colour of the flower). This is associated with malar erythema and oedema (Fig. 10.6) and, sometimes, less striking erythema of the neck and presternal area. Most patients also develop lilac slightly atrophic papules over the knuckles of their fingers (Gottron’s papules), streaks of erythema over the extensor tendons of the hand, peri-ungual telangiectasia and ragged cuticles (Fig. 10.7). The skin signs usually appear at the same time as the muscle symptoms but, occasionally, appear months or even years earlier. Sometimes, the skin signs appear in isolation. Many, but not all, patients have weakness of proximal muscles. Climbing stairs, getting up from chairs and combing the hair become difficult.

Course

In children the disorder is often self-limiting, but in adults it may be prolonged and progressive. Raynaud’s phenomenon, arthralgia, dysphagia and calcinosis may follow. The rash may become scaly and, rarely, itchy; eventually that on the light-exposed areas and overlying involved muscles develops poikiloderma (p. 252). Features of mixed connective disease (see below) may

Table 10.5 Some factors distinguishing the different types of LE.

<table>
<thead>
<tr>
<th></th>
<th>Antinuclear antibodies</th>
<th>Sun sensitivity</th>
<th>Internal organ involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic LE</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Subacute LE</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Discoid LE</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

Fig. 10.6 Acute dermatomyositis: oedematous purple face with erythema on presternal area. Severe progressive muscle weakness, but no underlying tumour was found.

Fig. 10.7 Erythema and telangiectasia of the nail folds are important clues to systemic connective tissue disorders. This patient has dermatomyositis. Note Gottron’s papules over the knuckles.
develop. The presence of calcinosis suggests a good prognosis.

Complications
Myositis may lead to permanent weakness and immobility, and inflammation to contractures or cutaneous calcinosis. Some die from progressive and severe myopathy.

Differential diagnosis
Other connective tissue disorders may look similar, particularly mixed connective tissue disease (p. 129) and SLE. In LE, the finger lesions favour the skin between the knuckles whereas in dermatomyositis the knuckles are preferred. Toxoplasmosis may cause a dermatomyositis-like syndrome. Myopathy can be a side-effect of systemic steroids, so weakness is not always caused by the disease itself.

Investigations
About 30% of adults with dermatomyositis also have an underlying malignancy. Their dermatomyositis coincides with the onset of the tumour and may improve if it is removed. Adult dermatomyositis or polymyositis therefore requires a search for such an underlying malignancy. The levels of muscle enzymes such as aldolase and creatine phosphokinase (CPK) are often elevated. Electromyography (EMG) detects muscle abnormalities, and biopsy of an affected muscle shows inflammation and destruction. Surprisingly, the ESR is often normal and antinuclear antibodies may not be detected. Toxoplasmosis should be excluded by serology.

Treatment
Systemic steroids, often in high doses (e.g. prednisolone 60 mg/day for an average adult; Formulary 2, p. 348), are the cornerstone of treatment and protect the muscles from destruction. A maintenance regimen may be needed for several years. Immunosuppressive agents, such as azathioprine (Formulary 2, p. 346), also help to control the condition and to reduce the high steroid dose. Cyclosporin (Formulary 2, p. 347) and methotrexate (Formulary 2, p. 348) have proved useful alternatives in stubborn cases. Maintenance treatment is adjusted according to clinical response and CPK level. As in SLE, intravenous gamma globulin infusions seem promising. Long-term and regular follow-up is necessary.

Systemic sclerosis
In this disorder the skin becomes hard as connective tissues thicken. Early in the condition, T-helper cells dominate the inflammatory infiltrate in the dermis and cause fibroblasts to proliferate and produce more hyaluronic acid and type I collagen (p. 16). In addition there is intimal thickening of arterioles and arteries. These processes are not confined to the skin, but involve many other organs, including the gut, lungs, kidneys and heart, leading to their dysfunction and to death.

The cause of systemic sclerosis is unknown but many, apparently unrelated, pieces of the complex jigsaw are now beginning to come together. A systemic sclerosis-like syndrome is a feature of the chronic graft-vs.-host disease sometimes seen after bone marrow transplantation (p. 286) and prolonged, untreated porphyria cutanea torda (p. 287). Similar syndromes have been reported following ingestion of adulterated rapeseed oil in Spain and dimerised L-tryptophan for insomnia and treatment with the antitumour agent, bleomycin. Environmental factors may also be relevant in isolated cases; changes like those of systemic sclerosis have affected workers exposed to polyvinyl chloride monomers, trichlorethylene and epoxy resins and in those subjected for years to severe vibration.

Presentation
Most patients suffer from Raynaud’s phenomenon (p. 135) and sclerodactyly. Their fingers become immobile, hard and shiny. Some become hyperpigmented and itchy early in their disease. Peri-ungual telangiectasia is common.
Investigations

The diagnosis is made clinically because histological abnormalities are seldom present until the physical signs are well established. Laboratory tests should include a fluorescent antinuclear antibody test and the evaluation of the heart, kidney, lungs, joints and muscles. Barium studies are best avoided as obstruction may follow poor evacuation. Other contrast media are available. X-rays of the hands, measurement of muscle enzymes and immunoglobulin levels, and a blood count, ESR and test for the scleroderma-associated antibody Scl-70 are also worthwhile.

Treatment

This is unsatisfactory. The calcium channel blocker nifedipine may help Raynaud’s phenomenon (p. 135). Systemic steroids, salicylates, antimalarials and long-term penicillin are used, but are not of proven value. D-penicillamine has many side-effects, especially on
CREST syndrome

This is a variant of systemic sclerosis with a relatively good prognosis associated often with serum antibodies to nuclear centromeres. The mnemonic stands for Calcinosis, Raynaud’s phenomenon, oEsophageal dysmotility, Sclerodactyly and Telangiectasia. Telangiectasia is peri-ungual on the fingers and flat, mat-like or rectangular on the face. Many patients with this syndrome develop a diffuse progressive systemic sclerosis after months or years.

Eosinophilic fasciitis

Localized areas of skin become indurated, sometimes after an upper respiratory tract infection or prolonged severe exercise. Hypergammaglobulinaemia and eosinophilia are present and a deep skin biopsy, which includes muscle, shows that the fascia overlying the muscle is thickened. Despite its name, and despite a profound eosinophilia in the peripheral blood, the
condition may cause stenosis of the urethral meatus, and adhesions between the foreskin and glans of the penis (see also Chapter 13).

**Mixed connective tissue disease**

This is an overlap between SLE and either scleroderma or polymyositis.

**Presentation**

As in LE, women are affected more often than men. Many develop swollen hands and sclerodactyly, and skin lesions like those of cutaneous LE may also be present. Alopecia is mild and the hair fall mimics telogen effluvium. Peri-ungual telangiectasia and pigmentary disturbances are common. About 25% of patients have a small vessel vasculitis with palpable purpura, leg ulcers and painful dermal nodules on the hands or elbows. Many show Raynaud’s phenomenon, arthritis, serositis and myositis. Headaches, weakness, fatigue, lymph node enlargement or hoarseness occur in about one in three patients; renal and central nervous system disease are less common.
These are always associated with the presence of rheumatoid factor. Some patients with rheumatoid arthritis have a vasculitis of larger blood vessels with deep ‘punched out’ ulcers on the legs (p. 106).

Reiter’s syndrome

Reiter’s syndrome, precipitated by non-specific urethritis or dysentery, combines skin lesions, arthropathy, conjunctivitis, balanitis, mucositis and spondylitis. Arthritis is the most severe element. The skin lesions (keratoderma blenorrhagicum) are psoriasis-like red scaling plaques, often studded with vesicles and pustules, seen most often on the feet. The toes are red and swollen, and the nails thicken. Psoriasiform plaques may also occur on the penis and scrotum, with redness near the penile meatus. Topical steroids and systemic NSAIDs help, but many patients need methotrexate (Formulary 2, p. 348) and/or systemic steroids.

Relapsing polychondritis

This process can affect any cartilage as the disorder is apparently caused by autoimmunity to collagen. The ears are the usual target. The overlying skin becomes red, swollen and tender. The cartilage in joints, the nose and the tracheo-bronchial tree may be involved, so that patients develop floppy ears, a saddle nose, hoarseness, stridor and respiratory insufficiency. Aortic aneurysms are also seen. Treatment is with systemic steroids and NSAIDs. Tracheostomy may be necessary.

Behçet’s syndrome

Behçet’s syndrome is discussed in Chapter 13.

Polyarteritis nodosa

This is discussed in Chapter 8 but is considered by some to be a connective tissue disorder.

Panniculitis

Panniculitis is an inflammation of the subcutaneous fat. It includes a number of diseases with different causes but a similar appearance: some are listed in Table 10.6.
Investigations

The type of panniculitis can sometimes be identified by skin biopsy, which must include subcutaneous fat. A complete blood count, ESR, chest X-ray, serum lipase, serum α1-antitrypsin and tests for antinuclear antibodies are needed.

Treatment

This depends upon the cause. Rest, elevation of affected extremities and local heat often help symptoms. NSAIDs may also bring help in the absence of specific therapy.

Further reading


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**Table 10.6 Causes of panniculitis.**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema nodosum (p. 101)</td>
</tr>
<tr>
<td>Erythema nodosum leprosum (leprosy)</td>
</tr>
<tr>
<td>Nodular vasculitis (p. 102)</td>
</tr>
<tr>
<td>Erythema induratum</td>
</tr>
<tr>
<td>Weber–Christian type</td>
</tr>
<tr>
<td>Polyarteritis nodosa (p. 104)</td>
</tr>
<tr>
<td>Associated with pancreatitis</td>
</tr>
<tr>
<td>Associated with SLE (lupus profundus)</td>
</tr>
<tr>
<td>Cold-induced</td>
</tr>
<tr>
<td>Withdrawal of systemic steroids</td>
</tr>
<tr>
<td>Superficial and migratory thrombophlebitis</td>
</tr>
<tr>
<td>Deficiency of α1-antitrypsin</td>
</tr>
<tr>
<td>Factitial (e.g. from injection of milk)</td>
</tr>
</tbody>
</table>

Presentation

Most patients have tender ill-defined red nodules on the lower legs, thighs and buttocks.

Course

This depends upon the cause. Migratory thrombophlebitis may be associated with underlying malignancy. In lupus profundus, a panniculitis is associated with discoid or SLE. Causes of erythema nodosum are discussed in Chapter 8. Erythema induratum may be caused by tuberculosis. Erythema nodosum leprosum is a reactional state in leprosy. Patients with pancreatitis may liberate enough lipase into the systemic circulation to cause fat in the skin to liquefy and discharge through the overlying skin. The Weber–Christian variant is associated with fever, but its cause is unknown.
In functional diseases of the blood and lymphatic vessels, abnormalities of flow are reversible, and there is no vessel wall damage (e.g. in urticaria; discussed in Chapter 8). The diseases of structure include the many types of vasculitis, some of which, with an immunological basis, are also covered in Chapter 8. For convenience, disorders of the blood vessels are grouped according to the size and type of the vessels affected.

**Disorders involving small blood vessels**

**Acrocyanosis**

This type of ‘poor circulation’, often familial, is more common in females than males. The hands, feet, nose, ears and cheeks become blue-red and cold. The palms are often cold and clammy. The condition is caused by arteriolar constriction and dilatation of the subpapillary venous plexus, and to cold-induced increases in blood viscosity. The best answers are warm clothes and the avoidance of cold.

**Erythrocyanosis**

This occurs in fat, often young, women. Purple-red mottled discoloration is seen over the buttocks, thighs and lower legs. Cold provokes it and causes an unpleasant burning sensation. An area of acrocyanosis or erythrocyanosis may be the site where other disorders will settle in the future, e.g. perniosis, erythema induratum, lupus erythematosus, sarcoidosis, cutaneous tuberculosis and leprosy.

**Perniosis (chilblains)**

In this common, sometimes familial, condition, inflamed purple-pink swellings appear on the fingers, toes and, rarely, ears (Fig. 11.1). They arrive with winter and are induced by cold. They are painful, anditchy or burning on rewarming. Occasionally they ulcerate. Chilblains are caused by a combination of arteriolar and venular constriction, the latter predominating on rewarming with exudation of fluid into the tissues. Warm housing and clothing help. Topical remedies rarely work, but the oral calcium channel blocker nifedipidine may be useful (p. 136). The blood pressure should be monitored at the start of treatment and at return visits. The vasodilator nicotinamide (500 mg three times daily) may be helpful alone or in addition to calcium channel blockers. Sympathectomy may be advised in severe cases.

**Erythromelalgia**

This is a rare condition in which the extremities become red, hot and painful when they or their owner are exposed to heat. The condition may be idiopathic,
Palmar erythema

This may be an isolated finding in a normal person or be familial. Sometimes it is seen in pregnancy, liver disease or rheumatoid arthritis. Often associated with spider telangiectases (see below), it may be caused by increased circulating oestrogens.

Erythema migrans (p. 195)

These annular erythematous areas are usually solitary, and occur most often on exposed skin after a tick bite. They expand slowly and may become very large.

Telangiectases

This term refers to permanently dilated and visible small vessels in the skin. They appear as linear, punctate or stellate crimson-purple markings. The common causes are given in Table 11.2.

Spider naevi

These stellate telangiectases do look rather like spiders, with legs radiating from a central, often palpable, feeding vessel. If the diagnosis is in doubt, press on the central feeding vessel with the corner of a glass slide and the entire lesion will disappear. Spider naevi are seen frequently on the faces of normal children, and may erupt in pregnancy or be the presenting sign of liver disease, with many lesions on the upper trunk. Liver function should be checked in those with many spider naevi. The central vessel can be destroyed by electrodessication without local anaesthesia or with a pulsed dye laser (p. 327).

Livedo reticularis

This cyanosis of the skin is net-like or marbled and caused by stasis in the capillaries furthest from their arterial supply: at the periphery of the inverted cone supplied by a dermal arteriole (see Fig. 2.1). ‘Cutis marmorata’ is the name given to the mottling of the skin seen in many normal children. It is physiological and disappears on warming, whereas true livedo reticularis remains.

The causes of livedo reticularis are listed in Table 11.3. Livedo vasculitis and cutaneous polyarteritis are

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Table 11.1 Classification of erythemas.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread</td>
<td>Caused by infection (bacterial or viral)</td>
</tr>
<tr>
<td></td>
<td>Drug reactions</td>
</tr>
<tr>
<td></td>
<td>Connective tissue diseases</td>
</tr>
<tr>
<td></td>
<td>Underlying malignancy (e.g. figurate erythema)</td>
</tr>
<tr>
<td></td>
<td>Idiopathic (‘toxic’ or ‘reactive’)</td>
</tr>
<tr>
<td>Localized</td>
<td>Pregnancy, liver disease, rheumatoid arthritis (causing palmar erythema)</td>
</tr>
<tr>
<td></td>
<td>Drug reaction (fixed drug eruption)</td>
</tr>
<tr>
<td></td>
<td>Infection (e.g. erythema chronicum migrans caused by <em>Borrelia burgdorferi</em>)</td>
</tr>
</tbody>
</table>

or caused by a myeloproliferative disease (e.g. polycythaemia rubra vera or thrombocythaemia), lupus erythematosus, rheumatoid arthritis, diabetes, degenerative peripheral vascular disease or hypertension. Small doses of aspirin give symptomatic relief. Alternatives include non-steroidal anti-inflammatory drugs (NSAIDs), α blockers and oxpentifylline (pentoxifylline).

Erythemas

Erythema accompanies all inflammatory skin conditions, but the term ‘the erythemas’ is usually applied to a group of conditions with redness but without primary scaling. Such areas are seen in some bacterial and viral infections such as toxic shock syndrome and measles. Drugs are another common cause (Chapter 22). If no cause is obvious, the rash is often called a ‘toxic’ or ‘reactive’ erythema (Table 11.1).

When erythema is associated with oedema (‘urticated erythema’) it becomes palpable.

Figurate erythemas

These are chronic eruptions, made up of bizarre serpiginous and erythematous rings. In the past most carried Latin labels; happily, these eruptions are now grouped under the general term of ‘figurate erythemas’. Underlying malignancy, a connective tissue disorder, a bacterial, fungal or yeast infection, worm infestation, drug sensitivity and rheumatic heart disease should be excluded, but often the cause remains obscure.
CHAPTER 11

forms of vasculitis associated with livedo reticularis (Chapter 8).

Antiphospholipid syndrome

Some patients with an apparently idiopathic livedo reticularis develop progressive disease in their peripheral, cerebral, coronary and renal arteries. Others, usually women, have multiple arterial or venous thrombo-embolic episodes accompanying livedo reticularis. Recurrent spontaneous abortions and intrauterine fetal growth retardation are also features. Prolongation of the activated partial thromboplastin time (APTT) and the presence of antiphospholipid antibodies (either anticardiolipin antibody or lupus anticoagulant, or both) help to identify this syndrome. Systemic lupus erythematosus should be excluded (Chapter 10).
be responsible for flushing as this can occur after hypophysectomy. It is possible that menopausal flushing is mediated by central mechanisms involving encephalins. Hot flushes can usually be helped by oestrogen replacement.

Alcohol-induced flushing is most commonly seen in oriental people. Ethanol is broken down to acetaldehyde by alcohol dehydrogenase and acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenase (Fig. 11.3). Acetaldehyde accumulation is in part responsible for flushing. Oriental people not only may have a high-activity variant of alcohol dehydrogenase but also defective aldehyde dehydrogenase. Disulfiram (Antabuse) and, to a lesser extent, chlorpropamide inhibit aldehyde dehydrogenase so that some individuals taking these drugs may flush.

Arterial disease

Raynaud’s phenomenon

This is a paroxysmal pallor of the digits provoked by cold or, rarely, emotional stress. At first the top of one or more fingers becomes white. On rewarming, a
5 days until a therapeutic dose is achieved (e.g. 5–20 mg three times daily) or until intolerable side-effects occur. The blood pressure should be monitored before each incremental increase in the dosage. Diltiazem (30–60 mg three times daily) is less effective than nifedipine but has fewer side-effects. Systemic vasodilators such as naftidrofuryl oxalate, nicotinic acid and thymoxamine (moxisylyte) are also worth trying. Glycerol trinitrate ointment, applied once daily may reduce the severity and frequency of attacks and may allow reduction in the dosage of calcium channel blockers and vasodilators. Infusions with reserpine or prostacyclin help some severe cases although occasionally sympathectomy is needed.

### Polyarteritis nodosa

This is discussed in Chapter 8.

### Temporal arteritis

Here the brunt is borne by the larger vessels of the head and neck. The condition affects elderly people and may be associated with polymyalgia rheumatica. The classical site is the temporal arteries, which...
become tender and pulseless, in association with severe headaches. Rarely, necrotic ulcers appear on the scalp. Blindness may follow if the ophthalmic arteries are involved, and to reduce this risk systemic steroids should be given as soon as the diagnosis has been made. In active phases the erythrocyte sedimentation rate (ESR) is high and its level can be used to guide treatment, which is often prolonged.

Atherosclerosis

This occlusive disease, most common in developed countries, will not be discussed in detail here, but involvement of the large arteries of the legs is of concern to dermatologists. It may cause intermittent claudication, nocturnal cramp, ulcers or gangrene. These may develop slowly over the years, or within minutes if a thrombus forms on an atheromatous plaque. The feet are cold and pale, the skin is often atrophic, with little hair, and peripheral pulses are diminished or absent.

Investigations should include urine testing to exclude diabetes mellitus. Fasting plasma lipids (cholesterol, triglycerides and lipoproteins) should be checked in the young, especially if there is a family history of vascular disease. Doppler ultrasound measurements help to distinguish atherosclerotic from venous leg ulcers in the elderly (p. 142). Complete assessment is best carried out by a specialist in peripheral vascular disease or a vascular surgeon.

Arterial emboli

Emboli may lodge in arteries supplying the skin and cause gangrene, ulcers or necrotic papules, depending on the size of the vessel obstructed. Causes include dislodged thrombi (usually from areas of atherosclerosis), fat emboli (after major trauma), infected emboli (e.g. gonococcal septicaemia or subacute bacterial endocarditis) and tumour emboli.

Pressure sores (Fig. 11.5)

Sustained or repeated pressure on skin over bony prominences can cause ischaemia and pressure sores. These are common in patients over 70 years old who are confined to hospital, especially those with a fractured neck of femur. The morbidity and mortality of those with deep ulcers is high.
1 Suitable investigations include venography, Doppler ultrasonography, which can only detect thrombi in large veins at, or above, the popliteal fossa, and $^{125}$I-fibrinogen isotope leg scanning.

Treatment is anticoagulation with heparin and later with a coumarin. The value of thrombolytic regimens has yet to be assessed properly. Prevention is important. Deep vein thrombosis after a surgical operation is less frequent now, with early postoperative mobilization, regular leg exercises, the use of elastic stockings over the operative period and prophylaxis with low dose heparin.

**Venous disease**

**Deep vein thrombosis**

The common causes are listed in Table 11.6.

The onset may be ‘silent’ or heralded by pain in the calf, often about 10 days after immobilization for surgery, parturition or an infection. The leg becomes swollen and cyanotic distal to the thrombus. The calf may hurt when handled or if the foot is dorsiflexed (Homan’s sign). Sometimes a pulmonary embolus is the first sign of a silent deep vein thrombosis.

**Thrombophlebitis**

This is thrombosis in an inflamed vein. If the affected vein is varicose or superficial it will be red and feel like a tender cord. The leg may be diffusely inflamed, making a distinction from cellulitis (p. 193) difficult. There may be fever, leucocytosis and a high ESR. Migratory superficial thrombophlebitis should arouse suspicion of an underlying malignancy or pancreatic disease.

Treatment is based on rest, local heat and NSAIDs. Antibiotics or anticoagulants rarely help.

---

**Table 11.6 Some causes of deep vein thrombosis.**

| Abnormalities of the vein wall | Trauma (operations and injuries) |
| Abnormalities of the vein wall | Chemicals (intravenous infusions) |
| Abnormalities of the vein wall | Neighbouring infection (e.g. in leg ulcer) |
| Abnormalities of the vein wall | Tumour (local invasion) |
| Abnormalities of blood flow | Stasis (immobility, operations, long aircraft flights, pressure, pregnancy, myocardial infarction, heart failure, incompetent valves) |
| Abnormalities of blood flow | Impaired venous return |
| Abnormalities of clotting | Platelets increased or sticky (thrombocythaemia, polycythaemia vera, leukaemia, trauma, splenectomy) |
| Abnormalities of clotting | Decreased fibrinolysis (postoperative) |
| Abnormalities of clotting | Deficiency of clotting factors (e.g. antithrombin, Proteins C and S, Factor V Leiden) |
| Abnormalities of clotting | Alteration in clotting factors (oral contraceptive, infection, leukaemia, pregnancy, shock and haemorrhage) |
| Abnormalities of clotting | Antiphospholipid antibody |
| Unknown mechanisms | Malignancy (thrombophlebitis migrans) |
| Unknown mechanisms | Smoking |
| Unknown mechanisms | Behçet’s syndrome |
| Unknown mechanisms | Inflammatory bowel disease |
BLOOD VESSEL AND LYMPHATIC DISORDERS

Venous hypertension, the gravitational syndrome and venous leg ulceration

Ulcers of the lower leg, secondary to venous hypertension, have an estimated prevalence of around 1%, are more common in women than in men, and account for some 85% of all leg ulcers seen in the UK and USA.

Cause

Satisfactory venous drainage of the leg requires three sets of veins: deep veins surrounded by muscles; superficial veins; and the veins connecting these together—the perforating or communicating veins (Fig. 11.6). When the leg muscles contract, blood in the deep veins is squeezed back, against gravity, to the heart (the calf muscle pump); reflux is prevented by valves. When the muscles relax, with the help of gravity, blood from the superficial veins passes into the deep veins via the communicating vessels. If the valves in the deep and communicating veins are incompetent, the calf muscle pump now pushes blood into the superficial veins, where the pressure remains high (‘venous hypertension’) instead of dropping during exercise. This persisting venous hypertension enlarges the capillary bed; white cells accumulate here and are then activated (by hypoxic endothelial cells), releasing oxygen free radicals and other toxic products which cause local tissue destruction and ulceration. The increased venous pressure also forces fibrinogen and α₂-macroglobulin out through the capillary walls; these macromolecules trap growth and repair factors so that minor traumatic wounds cannot be repaired and an ulcer develops. Patients with these changes develop lipodermatosclerosis (see below) and have a high serum fibrinogen and reduced blood fibrinolytic activity. Figure 11.7 shows the factors causing venous ulceration.

Clinical features

Venous hypertension is heralded by a feeling of heaviness in the legs and by pitting oedema. Other signs include:
1 red or bluish discoloration;
2 loss of hair;
3 brown pigmentation (mainly haemosiderin from the breakdown of extravasated red blood cells) and scattered petechiae;
4 atrophie blanche (ivory white scarring with dilatated capillary loops; Fig. 11.8); and
5 induration, caused by fibrosis and oedema of the dermis and subcutis—sometimes called ‘lipodermatosclerosis’.

Ulceration is most common near the medial malleolus (Fig. 11.9). In contrast to arterial ulcers, which are usually deep and round, with a punched out appearance, venous ulcers are often large but shallow, with prominent granulation tissue in their bases. Incompetent perforating branches (blowouts) between the superficial and deep veins are best felt with the patient standing. Under favourable conditions the exudative phase gives way to a granulating and healing phase, signalled by a blurring of the ulcer margin, ingrowth of skin from it, and the appearance of scattered small grey epithelial islands over the base. Prolonged ulceration, with lipodermatosclerosis, gives the leg the look of an inverted champagne bottle.

Complications

Bacterial superinfection is inevitable in a longstanding ulcer, but needs systemic antibiotics only if there is...
pyrexia, a purulent discharge, rapid extension or an increase in pain, cellulitis, lymphangitis or septicaemia.

Eczema (p. 90) is common around venous ulcers. Allergic contact dermatitis (p. 80) is a common complication and should be suspected if the rash worsens, itches or fails to improve with local treatment. Lanolin, parabens (a preservative) and neomycin are the most common culprits.

Malignant change can occur. If an ulcer has a hyperplastic base or a rolled edge, biopsy may be needed to rule out a squamous cell carcinoma (Fig. 11.10).

Differential diagnosis

The main causes of leg ulceration are given in Table 11.7. The most important differences between venous and other leg ulcers are the following.

* **Atherosclerotic.** These ulcers are more common on the toes, dorsum of foot, heel, calf and shin, and are unrelated to perforating veins. Their edges are often sharply defined, their outline may be polycyclic and the ulcers may be deep and gangrenous. Islands of intact skin are characteristically seen within the ulcer. Claudication may be present and peripheral pulses absent.

* **Vasculitic.** These ulcers start as painful palpable purpuric lesions, turning into small punched-out ulcers.
The involvement of larger vessels is heralded by painful nodules that may ulcerate. The intractable deep sharply demarcated ulcers of rheumatoid arthritis are caused by an underlying vasculitis (Fig. 11.11).

Thrombotic ulcers. Skin infarction (Fig. 11.12), leading to ulceration, may be caused by embolism or by the increased coagulability of polycythaemia or cryoglobulinaemia.

Infective ulcers. Infection is now a rare cause of leg ulcers in the UK but ulcers caused by tuberculosis, leprosy, atypical mycobacteria, diphtheria and deep fungal infections, such as sporotrichosis or chromoblastomycosis, are still seen in the tropics.

<table>
<thead>
<tr>
<th>Table 11.7 Causes of leg ulceration.</th>
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<tbody>
<tr>
<td><strong>Venous hypertension</strong></td>
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<tr>
<td><strong>Arterial disease</strong></td>
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<td><strong>Abnormalities of blood</strong></td>
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<td><strong>Infection</strong></td>
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<td><strong>Tumour</strong></td>
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<td><strong>Trauma</strong></td>
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**Panuliculitic ulcers.** These may appear at odd sites, such as the thighs, buttocks or backs of the calves. The most common types of panniculitis that ulcerate are lupus panuliculitis, pancreatic panniculitis and erythema induratum (p. 130).

**Malignant ulcers.** Those caused by a squamous cell carcinoma (p. 267) are the most common, but both malignant melanomas (p. 268) and basal cell carcinomas (p. 265) can present as flat lesions, which expand, crust and ulcerate. Furthermore, squamous cell carcinoma can arise in any longstanding ulcer, whatever its cause.

**Pyoderma gangrenosum** (p. 292). These large and rapidly spreading ulcers may be circular or polycyclic, and have a blue, indurated, undermined or pustular margin. Pyoderma gangrenosum may complicate rheumatoid arthritis, Crohn’s disease, ulcerative colitis or blood dyscrasias.

**Investigations**

Most chronic leg ulcers are venous, but other causes should be considered if the signs are atypical. In patients with venous ulcers, a search for contributory factors, such as obesity, peripheral artery disease, cardiac failure or arthritis, is always worthwhile. Investigations should include the following.

- Urine test for sugar.
- Full blood count to detect anaemia, which will delay healing.
- Swabbing for pathogens (see Bacterial superinfection above).
- Venography, colour flow duplex scanning and the measurement of ambulatory venous pressure help to detect surgically remediable causes of venous incompetence.
- Doppler ultrasound may help to assess arterial circulation when atherosclerosis is likely. It seldom helps if the dorsalis pedis or posterior tibial pulses can easily be felt. If the maximal systolic ankle pressure divided by the systolic brachial pressure (‘ankle brachial pressure index’) is greater than 0.8, the ulcer is unlikely to be caused by arterial disease.
- Cardiac evaluation for congestive failure.

**Treatment**

Venous ulcers will not heal if the leg remains swollen and the patient chair-bound. Pressure bandages take priority over other measures but not for atherosclerotic ulcers with an already precarious arterial supply. A common error is to use local treatment that is too elaborate. As a last resort, admission to hospital for elevation and intensive treatment may be needed, but the results are not encouraging; patients may stay in the ward for many months only to have their apparently well-healed ulcers break down rapidly when they go home.

The list of therapies is extensive. They can be divided into the following categories: physical, local, oral and surgical.

**Physical measures**

**Compression bandages and stockings**

Compression bandaging, with the compression graduated so that it is greatest at the ankle and least at the top of the bandage, is vital for most venous ulcers; it reduces oedema and aids venous return. The bandages are applied over the ulcer dressing, from the forefoot to just below the knee. Self-adhesive bandages (e.g. Secure Forte and Coban) are convenient and have largely replaced elasticated bandages. Bandages stay on for 2–7 days at a time and are left on at night. One four-layer compression bandaging system includes a layer of orthopaedic wool (Velband), a standard crepe, an elasticated bandage (e.g. Elset and Litepress) and an elasticated cohesive bandage (e.g. Secure Forte and Coban): it requires changing only once a week and is very effective. The combined four layers give a 40-mmHg compression at the ankle. Once an ulcer has healed, a graduated compression stocking (e.g. Duomed, Medi Strumpf, or Venosan 2502/2003 (UK) or Jobst or Teds (USA)) from toes to knee (or preferably thigh), should be prescribed, preferably at pressures of at least 35 mmHg. A foam or felt pad may be worn under the stockings to protect vulnerable areas against minor trauma. The stocking should be put on before rising from bed. Care must be taken with all forms of compression to ensure that the arterial supply is satisfactory and not compromised.
Elevation of the affected limb

Preferably above the hips, this aids venous drainage, decreases oedema and raises oxygen tension in the limb. Patients should rest with their bodies horizontal and their legs up for at least 2 h every afternoon. The foot of the bed should be raised by at least 15 cm; it is not enough just to put a pillow under the feet.

Walking

Walking, in moderation, is beneficial, but prolonged standing or sitting with dependent legs is not.

Physiotherapy

Some physiotherapists are good at persuading venous ulcers to heal. Their secret lies in a combination of the following: leg exercises, elevation, gentle massage, ultrasound treatment to the skin around the ulcers, oedema pumps and graduated compression bandaging.

Diet

Many patients are obese and should lose weight.

Local therapy

Remember that many ulcers will heal with no treatment at all but, if their blood flow is compromised, they will not heal despite meticulous care.

Local therapy should be chosen to:
• control or absorb the exudates;
• reduce the pain;
• control the odour;
• protect the surrounding skin;
• remove surface debris;
• promote re-epithelialization; and
• make optimal use of nursing time.

There are many preparations to choose from; those we have found most useful are listed in Formulary 1 (p. 338).

Clean ulcers (Fig. 11.13)

Dressings need be changed only once or twice a week, keeping the ulcer moist. Paraffin tulle dressings, plain or impregnated with 0.5% chlorhexidine, 0.25% silver proteinate in compound calamine cream spread on a non-stick dressing, 1% silver sulphadiazine cream, and simple zinc and castor oil ointment, are all helpful and easy to apply. The area should be cleaned gently with arachis oil, 5% hydrogen peroxide or saline before the next dressing is applied. Sometimes immersing the whole ulcer in a tub of warm water helps to loosen or dissolve adherent crusts. The prolonged use of antiseptics may be harmful.

Many dressings have absorbent and protective properties (Formulary 1, p. 338). These include Granuflex and DuoDERM Extra Thin (which have the advantage of sticking to the surrounding skin), Geliperm, Kaltostat and Sorbsan in the UK and Duoderm, Opsite and Tegaderm in the USA. Actisorb (UK) is a useful charcoal dressing that absorbs exudate and minimizes odour. Ointments containing recombinant human platelet growth factor may aid revascularization.

Medicated bandages (Formulary 1, p. 338) based on zinc paste, with ichthammol, or with calamine and clioquinol, are useful when there is much surrounding eczema, and can be used for all types of ulcers, even infected exuding ones. The bandage is applied in strips from the foot to below the knee. Worsening of eczema under a medicated bandage may signal
moderate strength local steroids, which must never be put on the ulcer itself. Lassar’s paste, zinc cream or paste bandages (see above) are suitable alternatives.

**Oral treatment**

The following may be helpful.

**Diuretics.** Pressure bandaging is more important as the oedema associated with venous ulceration is largely mechanical. Diuretics will combat the oedema of cardiac failure.

**Analgesics.** Adequate analgesia is important. Aspirin may not be well tolerated by the elderly. Paracetamol (not available in the USA), or acetaminophen is often adequate but dihydrocodeine may be required. Analgesia may be needed only when the dressing is changed.

**Antibiotics.** Ulcers need not be ‘sterilized’ by local or systemic antibiotics. Short courses of systemic antibiotics should be reserved for spreading infections (see under Complications above) but are sometimes tried for pain or even odour. Bacteriological guidance is needed and the drugs used include erythromycin and flucloxacillin (streptococcal or staphylococcal cellulitis), metronidazole (*Bacteroides* infection) and ciprofloxacin (*Pseudomonas aeruginosa* infection). Bacterial infection may prejudice the outcome of skin grafting.

**Ferrous sulphate and folic acid.** For anaemia.

**Zinc sulphate.** May help to promote healing, especially if the plasma zinc level is low.

**Oxypentifylline** (pentoxyfylline) is fibrinolytic, increases the deformability of red and white blood cells, decreases blood viscosity and diminishes platelet adhesiveness. It may speed the healing of venous ulcers if used with compression bandages.

**Stanozolol.** This anabolic steroid may not heal an existing ulcer more quickly, but may prevent ulceration in lipodermatosclerosis and may protect against recurrences. The manufacturer’s advice on contraindications, e.g. prostatic cancer and abnormal liver function, and on monitoring treatment must not be overlooked.

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*Fig. 11.14* Infected ulcer with sloughing. Tendon visible at bottom of figure. Hospital admission and frequent dressings needed to save leg.

the development of allergic contact dermatitis to a component of the paste, most often parabens (a preservative) or cetostearyl alcohols.

**Infected ulcers** (Fig. 11.14)

These have to be cleaned and dressed more often than clean ones, sometimes even twice daily. Useful preparations include 0.5% silver nitrate, 0.25% sodium hypochlorite, 0.25% acetic acid, potassium permanganate (1 in 10 000 dilution) and 5% hydrogen peroxide, all made up in aqueous solution, and applied as compresses with or without occlusion. Helpful creams and lotions include 1.5% hydrogen peroxide, 20% benzoyl peroxide, 1% silver sulphadiazine, 10% povidone-iodine (Formulary 1, p. 338). The main function of dextran polymer beads, and starch polymer beads within cadexomer iodine, is to absorb exudate. Although antibiotic tulles are easy to apply and are well tolerated, they should not be used for long periods as they can induce bacterial resistance and sensitise. Resistance is not such a problem with povidone-iodine, and a readily applied non-adherent dressing impregnated with this antiseptic may be useful. Surrounding eczema is helped by weak or
Purpura (Fig. 11.15), petechiae and ecchymoses may be caused by a coagulation or platelet disorder, or by an abnormality of the vessel wall or the surrounding dermis. Some common causes are listed in Table 11.8. In general, coagulation defects give rise to ecchymoses and external bleeding. Platelet defects present more often as purpura, although bleeding and ecchymoses can still occur. Vasculitis of small vessels causes purpura, often palpable and painful, but not bleeding; this is discussed in Chapter 8. Purpura from vasodilatation and gravity is seen in many diseases of the legs, especially in the elderly (defective dermis around the blood vessels), and seldom requires extensive investigation.

Cryoglobulinaemia is a rare cause of purpura, which is most prominent on exposed parts. It may also cause cold urticaria (p. 95) and livedo reticularis (p. 133).
CHAPTER 11

**Coagulation defects**
Inherited defects (e.g. haemophilia, Christmas disease)
Connective tissue disorders
Disseminated intravascular coagulation
Paraproteinaemias (e.g. macroglobulinaemia)
Acquired defects (e.g. liver disease, anticoagulant therapy, vitamin K deficiency, drugs)

**Platelet defects**
Thrombocytopenia
  - Idiopathic
  - Connective tissue disorders, especially lupus erythematosus
  - Disseminated intravascular coagulation
  - Haemolytic anaemia
  - Hypersplenism
  - Giant haemangiomas (Kasabach–Merritt syndrome)
  - Bone marrow damage (cytostatic drugs, leukaemia, carcinoma)
  - Drugs (quinine, aspirin, thiazides and sulphamides)
Abnormal function
  - von Willebrand’s disease
Drugs (e.g. aspirin)

**Vascular defect**
Raised intravascular pressure (coughing, vomiting, venous hypertension, gravitational)
Vasculitis (including Henoch–Schönlein purpura)
Infections (e.g. meningococcal septicaemia, Rocky Mountain spotted fever)
Drugs (carbromal, aspirin, sulphamides, quinine, phenylbutazone and gold salts)
Painful bruising syndrome

**Idiopathic**
Progressive pigmented dermatoses (Fig. 11.16)

**Lack of support from surrounding dermis**
Senile purpura
Topical or systemic corticosteroid therapy
Scurvy (perifollicular purpura)
Lichen sclerosus et atrophicus
Systemic amyloidosis

The condition may be idiopathic, or secondary to myeloma, leukaemia, a previous hepatitis C infection or an autoimmune disease.

**Investigations**
The most common cause of purpura is trauma, especially to the thin sun-damaged skin of elderly forearms. When purpura has no obvious cause, investigations should include a platelet count, prothrombin time, activated partial thromboplastin time (APTT), a full blood count and biochemical screen. Electrophoresis is needed to exclude hypergammaglobulinaemia and paraproteinaemia. Cryoglobulinaemia should also be excluded. To help detect a consumptive coagulopathy, a coagulation screen, including measurement of fibrinogen and fibrin degradation products, may be necessary. The bleeding time, and a Hess tourniquet test for capillary fragility, help less often. Skin biopsy will confirm a small vessel vasculitis, if the purpura is palpable.
BLOOD VESSEL AND LYMPHATIC DISORDERS

Table 11.9 Causes of secondary lymphoedema.

<table>
<thead>
<tr>
<th>Cause</th>
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<tr>
<td>Recurrent lymphangitis</td>
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<tr>
<td>Lymphatic obstruction</td>
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<tr>
<td>Lymphatic destruction</td>
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<tr>
<td>Uncertain aetiology</td>
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</table>

| Erysipelas                 |
| Filariasis                 |
| Granuloma inguinale        |
| Tuberculosis               |
| Tumour                     |
| Surgery                    |
| Radiation therapy          |
| Tumour                     |
| Rosacea                    |
| Melkersson–Rosenthal syndrome (facial nerve palsy, fissuring of tongue and lymphoedema of lip) |
| Yellow nail syndrome       |

Cause

Lymphoedema may be primary or secondary. The primary forms are developmental defects, although signs may only appear in early puberty or even in adulthood. Sometimes lymphoedema involves only one leg. Secondary causes are listed in Table 11.9.

Treatment

Elevation, graduated compression bandages and stockings (p. 142), diuretics and the early treatment of lymphangitis or erysipelas are the cornerstones of treatment. If erysipelas recurs, long-term penicillin should be given. Surgery occasionally helps to remove an obstruction or restore drainage.

Lymphangitis

This streptococcal infection of the lymphatics may occur without any lymphoedema. A tender red line extends proximally. Penicillin flucloxacillin, cephalexin and erythromycin are usually effective.

Disorders of the lymphatics

Lymphoedema

The skin overlying chronic lymphoedema is firm and pits poorly. Longstanding lymphoedema may lead to gross, almost furry, hyperkeratosis, as in the so-called ‘mossy foot’.

Further reading


**Sebaceous glands**

Most sebaceous glands develop embryologically from hair germs, but a few free glands arise from the epidermis. Those associated with hairs lie in the obtuse angle between the follicle and the epidermis (Fig. 13.1). The glands themselves are multilobed and contain cells full of lipid, which are shed whole (holocrine secretion) during secretion so that sebum contains their remnants in a complex mixture of triglycerides, fatty acids, wax esters, squalene and cholesterol. Sebum is discharged into the upper part of the hair follicle. It lubricates and waterproofs the skin, and protects it from drying; it is also mildly bacteriocidal and fungistatic. Free sebaceous glands may be found in the eyelid (meibomian glands), mucous membranes (Fordyce spots), nipple, peri-anal region and genitalia.

Androgenic hormones, especially dihydrotestosterone, stimulate sebaceous gland activity. Human sebaceous glands contain 5α-reductase, 3α- and 17α-hydroxy steroid dehydrogenase, which convert weaker androgens to dihydrotestosterone, which in turn binds to specific receptors in sebaceous glands, increasing sebum secretion. The sebaceous glands react to maternal androgens for a short time after birth, and then lie dormant until puberty when a surge of androgens produces a sudden increase in sebum excretion and sets the stage for acne.

**Acne**

Acne is a disorder of the pilosebaceous apparatus characterized by comedones, papules, pustules, cysts and scars.

**Prevalence**

Nearly all teenagers have some acne (acne vulgaris).

It affects the sexes equally, starting usually between the ages of 12 and 14 years, tending to be earlier in females. The peak age for severity in females is 16–17 and in males 17–19 years. Variants of acne are much less common.

**Cause**

**Acne vulgaris**

Many factors combine to cause acne (Fig. 12.1), characterized by chronic inflammation around pilosebaceous follicles.

- **Sebum.** Sebum excretion is increased. However, this alone need not cause acne; patients with acromegaly, or with Parkinson’s disease, have high sebum excretion rates but no acne. Furthermore, sebum excretion often remains high long after the acne has gone away.

- **Hormonal.** Androgens (from the testes, ovaries and adrenals) are the main stimulants of sebum excretion, although other hormones (e.g. thyroid hormones and growth hormone) have minor effects too. Those castrated before puberty never develop acne. In acne, the sebaceous glands respond excessively to what are usually normal levels of these hormones (increased target organ sensitivity). This may be caused by 5α-reductase activity being higher in the target sebaceous glands than in other parts of the body. Fifty per cent of females with acne have slightly raised free testosterone levels—usually because of a low level of sex hormone binding globulin rather than a high total testosterone—but this is still only a fraction of the concentration in males, and its relevance is debatable.

- **Poral occlusion.** Both genetic and environmental factors (e.g. some cosmetics) cause the epithelium to overgrow the follicular surface. Follicles then retain sebum that has an increased concentration of bacteria.
and free fatty acids. Rupture of these follicles is associated with intense inflammation and tissue damage, mediated by oxygen free radicals and enzymes such as elastase, released by white cells.

- **Bacterial.** *Propionibacterium acnes*, a normal skin commensal, plays a pathogenic part. It colonizes the pilosebaceous ducts, breaks down triglycerides releasing free fatty acids, produces substances chemotactic for inflammatory cells and induces the ductal epithelium to secrete pro-inflammatory cytokines. The inflammatory reaction is kept going by a type IV immune reaction (p. 26) to one or more antigens in the follicle.

- **Genetic.** The condition is familial in about half of those with acne. There is a high concordance of the sebum excretion rate and acne in monozygotic, but not dizygotic, twins. Further studies are required to determine the precise mode of inheritance.

**Variants of acne**

- **Infantile acne** may follow transplacental stimulation of a child’s sebaceous glands by maternal androgens.

- **Mechanical.** Excessive scrubbing, picking, or the rubbing of chin straps or a fiddle (see Fig. 12.2) can rupture occluded follicles.

- **Acne associated with virilization,** including clitoromegaly, may be caused by an androgen-secreting tumour of the adrenals, ovaries or testes or, rarely, to congenital adrenal hyperplasia caused by mild 21-hydroxylase deficiency. The gene frequency for this autosomal recessive disorder is high in Ashkenazi

**Fig. 12.1** Factors causing acne.

**Fig. 12.2** Papulopustular lesions in an odd distribution. The patient played the violin (‘fiddler’s neck’).
Jews (19%), inhabitants of the former Yugoslavia (12%) and Italians (6%).

- **Acne accompanying the polycystic ovarian syndrome** is caused by modestly raised circulating androgen levels.
- **Drug-induced.** Corticosteroids, androgenic and anabolic steroids, gonadotrophins, oral contraceptives, lithium, iodides, bromides, antituberculous and anticonvulsant therapy can all cause an acneiform rash.
- **Tropical.** Heat and humidity are responsible for this variant, which affects Caucasoids with a tendency to acne.
- **Acne cosmetica** (see p. 151).

### Presentation

**Common type**

Lesions are confined to the face, shoulders, upper chest and back. Seborrhoea (a greasy skin; Fig. 12.3) is often present. Open comedones (blackheads), because of the plugging by keratin and sebum of the pilosebaceous orifice, or closed comedones (whiteheads), caused by overgrowth of the follicle openings by surrounding epithelium, are always seen. Inflammatory papules, nodules and cysts (Figs 12.4 and 12.5) occur, with one or two types of lesion predominating. Depressed or hypertrophic scarring and postinflammatory hyperpigmentation can follow.

Conglobate (gathered into balls; from the Latin *globus* meaning ‘ball’) is the name given to a severe form of acne with all of the above features as well as abscesses or cysts with intercommunicating sinuses that contain thick serosanguinous fluid or pus. On resolution, it leaves deeply pitted or hypertrophic scars, sometimes joined by keloidal bridges. Although hyperpigmentation is usually transient, it can persist, particularly in those with an already dark skin.

Psychological depression is common in persistent acne, which need not necessarily be severe.

### Variants

- **Infantile.** This rare type of acne is present at, or appears soon after birth. It is more common in males and may last up to 3 years. Its morphology is like that of common acne (Fig. 12.6) and it may be the forerunner of severe acne in adolescence.
• **Polycystic ovarian syndrome.** Consider this in obese females with oligomenorrhoea or secondary amenorrhoea or infertility. Glucose intolerance, dyslipidaemia and hypertension may be other features.

• **Congenital adrenal hyperplasia.** Hyperpigmentation, ambiguous genitalia, history of salt-wasting in childhood, and a Jewish background, are all clues to this rare diagnosis.

• **Fulminans.** Acne fulminans is a rare variant in which conglobate acne is accompanied by fever, joint pains and a high erythrocyte sedimentation rate (ESR).

• **Exogenous.** Tars, chlorinated hydrocarbons, oils, and oily cosmetics can cause or exacerbate acne. Suspicion should be raised if the distribution is odd or if comedones predominate (Fig. 12.7).

• **Excoriated.** This is most common in young girls. Obsessional picking or rubbing leaves discrete denuded areas.

• **Late onset.** This too occurs mainly in women and is often limited to the chin (Fig. 12.8). Nodular and cystic lesions predominate. It is stubborn and persistent.

• **Acne associated with suppurative hidradenitis and perifolliculitis of scalp** (see below).

• **Tropical.** This occurs mainly on the trunk and may be conglobate.

• **Drug-induced** (Fig. 12.9). Suspicion should be raised when acne, dominated by papulo-pustules rather than comedones, appears suddenly in a non-teenager and coincides with the prescription of a drug known to cause acneiform lesions (see above). Some athletes still use anabolic steroids to enhance their performance.
17-hydroxyprogesterone, urinary free cortisol and, depending on the results, ultrasound examination or computed tomography scan of the ovaries and adrenals. Congenital adrenal hyperplasia is associated with high levels of 17-hydroxyprogesterone, and androgen-secreting tumours with high androgen levels.

Polycystic ovarian syndrome is characterized by modestly elevated testosterone, androstenedione and dehydroepiandrosterone sulphate levels, a reduced sex hormone-binding level and a LH : FSH ratio of greater than 2.5 : 1. Pelvic ultrasound may reveal multiple small ovarian cysts, although some acne patients have ovarian cysts without biochemical evidence of the polycystic ovarian syndrome.

**Differential diagnosis**

Rosacea (see below) affects older individuals; comedones are absent; the papules and pustules occur only on the face; and the rash has an erythematous background. Pyogenic folliculitis can be excluded by culture. Hidradenitis suppurativa (see below) is associated with acne conglobata, but attacks the axillae and groin. Pseudofolliculitis barbae, caused by ingrowing hairs, occurs on the necks of men with curly facial hair and clears up if shaving is stopped.

**Treatment**

Acne frequently has marked psychological effects. Even those with mild acne need sympathy. An optimistic approach is essential, and regular encouragement worthwhile.

Occasionally an underlying cause (see above) is found; this should be removed or treated.

At some time most teenagers try antiacne preparations bought from their pharmacist; local treatment is enough for most patients with comedo-papular acne, although both local and systemic treatment are needed for pustulocystic scarring acne (Fig. 12.10).

**Local treatment** (Formulary 1, p. 336)

1. **Regular gentle cleansing** with soap and water should be encouraged, to remove surface sebum. Antibacterial cleansers are also useful, e.g. chlorhexidine.
2. **Benzoyl peroxide.** This antibacterial agent is applied only at night initially, but can be used twice daily if this does not cause too much dryness and irritation. It is most effective for inflammatory lesions.
Azelaic acid is bacteriocidal for *P. acnes*: it is also anti-inflammatory and inhibits the formation of comedones by reducing the proliferation of keratinocytes. It should be applied twice daily, but not used for more than 6 months at a time.

Abrasive pastes containing aluminium oxide have largely been replaced by topical retinoids as aggressive scrubbing can rupture comedones.

Sulphur. A number of time-honoured preparations containing sulphur are available on both sides of the Atlantic. Some are included in Formulary 1 (p. 336).

Local antibiotics. These include topical clindamycin, erythromycin and sulfacetamide (Formulary 1, p. 336).

Combinations. Some combinations work better than either of the drugs used separately. Erythromycin combined with a zinc acetate complex (Formulary 1, p. 336) is popular and effective. It works as an antimicrobial, an inhibitor of 5α-reductase (see above), an antioxidant and as an immunomodulator. Erythromycin and clindamycin, in mixtures with benzoyl peroxide, reduce *P. acnes* numbers and the likelihood of resistant strains emerging (Formulary 1, p. 336).

Aluminium chloride. Alcoholic solutions of aluminium chloride, used as antiperspirants, may help tropical acne.

Cosmetic camouflage. Cover-ups help some patients, especially females, whose scarring is unsightly. They also obscure postinflammatory pigmentation. A range of make-ups is available in the UK and USA (Formulary 1, p. 330).
Trimethoprim is used by some as a third-line antibiotic for acne, when a tetracycline and erythromycin have not helped. White blood cell counts should be monitored. Ampicillin is another alternative.

Hormonal. A combined antiandrogen–oestrogen treatment (Dianette: 2 mg cyproterone acetate and 0.035 mg ethinylestradiol) is available in many countries and may help persistent acne in women. Monitoring is as for any patient on an oral contraceptive, and further contraceptive measures are unnecessary. Courses last for 8–12 months and the drug is then replaced by a low oestrogen/low progestogen oral contraceptive. These drugs are not for males.

A triphasic pill, or a pill with a high oestrogen content, is best for women with acne who also require oral contraception. Those on antibiotics should be warned of their possible interaction with oral contraceptives and should use other contraceptive precautions, especially if the antibiotics induce diarrhoea.

Isotretinoin (13-cis-retinoic acid, Formulary 2, p. 350). This is an oral retinoid, which inhibits sebum excretion, the growth of P. acnes, and acute inflammatory processes. The drug is reserved for severe nodulocystic acne, unresponsive to the measures outlined above. It is routinely given for 4–6 months only, in a dosage of 0.5–1 mg/kg body weight/day; young men with truncal acne usually require the higher dosage. A full blood count, liver function tests and fasting lipid levels should be checked, and routine urine analysis performed before the start of the course, and then at 4 weeks after starting the drug. Some physicians also monitor at 10 and 16 weeks and perform a final check 1 month after completing the course. The drug seldom has to be stopped, although rarely abnormalities of liver function limit treatment.

Isotretinoin is highly teratogenic: before starting treatment women should sign a form confirming that, as far as they know, they are not pregnant and that they have been warned about this risk. They should take an oral contraceptive or Dianette for 2 months before starting isotretinoin, throughout treatment and for 1 month thereafter. Tests for pregnancy, preferably performed on a blood sample, should be carried out twice before starting treatment and at follow-up visits. Contraception and teratogenicity of the drug must be discussed at all visits. The recommendations in the USA are especially stringent. Before receiving

Erythromycin (dosage as for oxytetracycline) is the next antibiotic of choice but is preferable to tetracyclines in women who might become pregnant. Its major drawback is the development of resistant Propionibacteria, now present in at least one in four patients with acne, which leads to therapeutic failure.

Systemic treatment (Formulary 2, p. 340)
Antibiotics: tetracyclines

• Oxytetracycline and tetracycline. An average starting dosage for an adult is 250 mg up to four times daily, but up to 1.5 g/day may be needed in resistant cases. The antibiotic should not be used for less than 3 months and may be needed for a year or two, or even longer. It should be taken on an empty stomach, 1 h before meals, or 4 h after food, as the absorption of these tetracyclines is decreased by milk, antacids and calcium, iron and magnesium salts. The dosage should be tapered in line with clinical improvement, an average maintenance dosage being 250–500 mg/day. Even with long courses, serious side-effects are rare, although candidal vulvovaginitis may force a change to a narrower spectrum antibiotic such as erythromycin.

• Minocycline, 50 mg twice daily or 100 mg once or twice daily (in a modified release preparation) is now preferred by many dermatologists, although it is much more expensive. Absorption is not significantly affected by food or drink. Minocycline is much more lipophilic than oxytetracycline and so probably concentrates better in the sebaceous glands. It is bacteriologically more effective than oxytetracycline and tetracycline and, unlike erythromycin, little resistance to it by Propionibacteria has been recorded. It can be effective even when oxytetracycline has failed, but can cause abnormalities of liver function and a lupus-like syndrome.

• Doxycycline, 100 mg once or twice daily is a cheaper alternative to minocycline, but more frequently associated with phototoxic skin reactions.

Tetracyclines should not be taken in pregnancy or by children under 12 years as they are deposited in growing bone and developing teeth, causing stained teeth and dental hypoplasia. Rarely, the long-term administration of minocycline causes a greyish pigmentation, like a bruise, especially on the faces of those with actinic damage and over the shins.
Other side-effects of isotretinoin include a dry skin, dry and inflamed lips and eyes, nosebleeds, facial erythema, muscle aches, hyperlipidaemia and hair loss; these are reversible and often tolerable, especially if the acne is doing well. Rarer and potentially more serious side-effects include changes in night-time vision and hearing loss. Occasionally, isotretinoin flares acne at first, but this effect is usually short lived and the drug can be continued. It is because of its early side-effects that some dermatologists start isotretinoin in a low dose (e.g. 20 mg/day) and then work up to the target dose if no significant side-effects are reported at review during the first month of treatment. Early review appointments (e.g. at 1 and 2 weeks into treatment) are comforting to both patient and doctor. A useful ‘avoidance list’ for patients taking isotretinoin is given in Table 12.1.

**Diet**

It is sensible for patients to avoid foods (e.g. nuts, chocolates, dairy products and wine) that they think make their acne worse, but there is little evidence that any dietary constituent, except iodine, causes acne.

**Physical**

_Ultraviolet B radiation_ therapy often helps with exacerbations. Two-month courses, during which the patient attends two or three times weekly, are usually adequate. _Cysts_ can be incised and drained with or without a local anaesthetic.

_Intralesional injections_ of 0.1 mL of triamcinolone acetonide (2.5–10 mg/mL) hasten the resolution of stubborn cysts, but can leave atrophy.
treatment is extended. In expert hands the results can be dramatic.

Collagen injections. Bovine collagen can be injected into depressed scars to improve their appearance. Patients with a history of any autoimmune disorder are excluded from this treatment. Shallow atrophic lesions do better than discrete ‘ice-pick’ scars. The procedure is expensive and has to be repeated every 6 months as the collagen is resorbed.

Rosacea

Rosacea affects the face of adults, usually women. Although its peak incidence is in the thirties and forties, it can also be seen in the young or old. It may coexist with acne but is distinct from it.

Cause and histopathology

The cause is still unknown. Rosacea is often seen in those who flush easily in response to warmth, spicy food, alcohol or embarrassment. Any psychological abnormalities, including neuroticism and depression, are secondary to the skin condition. No pharmacological defect has been found which explains these flushing attacks. Sebum excretion rate and skin microbiology are normal. A pathogenic role for the hair follicle mite, *Demodex folliculorum*, has not been proved.

Clinical course and complications

The cheeks, nose, centre of forehead, and chin are most commonly affected; the peri-orbital and peri-oral areas are spared (Fig. 12.12). Intermittent flushing is followed by a fixed erythema and telangiectases. Discrete domed inflamed papules, papulopustules and, rarely, nodules develop later. Rosacea, unlike acne, has no comedones or seborrhoea. It is usually symmetrical. Its course is prolonged, with exacerbations and remissions. Complications include blepharitis, conjunctivitis and, occasionally, keratitis. Rhinophyma, caused by hyperplasia of the sebaceous glands and connective tissue on the nose, is a striking complication (Fig. 12.13) that is more common in males. Lymphoedema, below the eyes and on the forehead, is a tiresome feature in a few cases. Some patients treated with potent topical steroids develop a rebound flare of pustules, worse than the original rosacea, when this treatment is stopped.
Differential diagnosis

Acne has already been mentioned. Rosacea differs from it by its background of erythema and telangiectases, and by the absence of comedones. The distribution of the lesions is different too, as rosacea affects the central face but not the trunk. Also rosacea usually appears after adolescence. Seborrhoeic eczema, perioral dermatitis (Fig. 12.14), systemic lupus erythematosus (p. 119) and photodermatitis should be considered, but do not show the papulopustules of rosacea. The flushing of rosacea can be confused with menopausal symptoms and, rarely, with the carcinoid syndrome. Superior vena caval obstruction has occasionally been mistaken for lymphoedematous rosacea.

Treatment

Tetracyclines, prescribed as for acne (p. 154), are the traditional treatment and are usually effective. Erythromycin is the antibiotic of second choice. Courses should last for at least 10 weeks and, after gaining control with 500–1000 mg daily, the dosage can be
zinc cream. Sunscreens may help if sun exposure is an aggravating factor, but changes in diet or drinking habits are seldom of value.

**Sweat glands**

**Eccrine sweat glands**

There are 2–3 million sweat glands distributed all over the body surface but they are most numerous on the palms, soles and axillae. The tightly coiled glands lie deep in the dermis, and the emerging duct passes to the surface by penetrating the epidermis in a corkscrew fashion. Sweat is formed in the coiled gland by active secretion, involving the sodium pump. Some damage occurs to the membrane of the secretory cells during sweating. Initially sweat is isotonic with plasma but, under normal conditions, it becomes hypotonic by the time it is discharged at the surface, after the tubular resorption of electrolytes and water under the influence of aldosterone and antidiuretic hormone.

In some ways the eccrine sweat duct is like a renal tubule. The pH of sweat is between 4.0 and 6.8; it contains sodium, potassium chloride, lactate, urea and ammonia. The concentration of sodium chloride in sweat is increased in cystic fibrosis, and sweat can be analysed when this is suspected.

Sweat glands have an important role in temperature control, the skin surface being cooled by evaporation. Up to 10 L/day of sweat can be excreted. Three stimuli induce sweating.

1. **Thermal sweating** is a reflex response to a raised environmental temperature and occurs all over the body, especially the chest, back, forehead, scalp and axillae.
2. **Emotional sweating** is provoked by fear or anxiety and is seen mainly on the palms, soles and axillae.
3. **Gustatory sweating** is provoked by hot spicy foods and affects the face.

The eccrine sweat glands are innervated by cholinergic fibres of the sympathetic nervous system. Sweating can therefore be induced by cholinergic, and blocked by anticholinergic drugs. Central control of sweating resides in the preoptic hypothalamic sweat centre.

Clinical disorders can follow increased or decreased sweating, or blockage of sweat gland ducts.
Generalized hyperhidrosis

**Thermal hyperhidrosis**

The ‘thermostat’ for sweating lies in the preoptic area of the hypothalamus. Sweating follows any rise in body temperature, whether this is caused by exercise, environmental heat or an illness. The sweating in acute infections, and in some chronic illnesses (e.g. Hodgkin’s disease), may be a result of a lowering of the ‘set’ of this thermostat.

**Other causes of general hyperhidrosis**

- Emotional stimuli, hypoglycaemia, opiate withdrawal, and shock cause sweating by a direct or reflex stimulation of the sympathetic system at hypothalamic or higher centres. Sweating accompanied by a general sympathetic discharge occurs on a cold pale skin.
- Lesions of the central nervous system (e.g. a cerebral tumour or cerebrovascular accident) can cause generalized sweating, presumably by interfering directly with the hypothalamic centre.
- Phaeochromocytoma, the carcinoid syndrome, diabetes mellitus, thyrotoxicosis, Cushing’s syndrome and the hot flushes of menopausal women have all been associated with general sweating. The mechanisms are not clear.

**Local hyperhidrosis** (Fig. 12.16)

Local hyperhidrosis plagues many young adults. The most common areas to be affected are the palms, soles and axillae. Too much sweating there is embarrassing, if not socially crippling. A sodden shirt in contact with a dripping armpit, a wet handshake and stinking feet are hard crosses to bear. Seldom is any cause found, but organic disease, especially thyrotoxicosis, acromegaly, tuberculosis and Hodgkin’s disease should be considered. A blatant anxiety state is occasionally present, but more often an otherwise normal person is understandably concerned about his or her antisocial condition. A vicious circle emerges, in which increased anxiety drives further sweating.

These problems may be no more than one end of the normal physiological range. How many students sitting examinations have to dry their hands before putting pen to paper? It is only when the sweating is gross, or continuous, that medical advice is sought. Such sweating is often precipitated by emotional stimuli and stops during sleep.

**Treatment**

**Topical applications.** The most useful preparation for axillary hyperhidrosis is 20% aluminium chloride hexahydrate in an alcohol base (Formulary 1, p. 331). At first it is applied to the dry axillae every night. Soon the interval can be increased, and many need the preparation only once or twice a week. The frequency may have to be cut down if the preparation irritates the skin, which is most likely if it is applied after shaving or when the skin is wet. Aluminium chloride also helps hyperhidrosis of the palms and soles, but it is less effective there.

Potassium permanganate soaks (1 : 10 000 aqueous solution) combat the bacterial superinfection of sweaty feet that is responsible for their foul smell. Patients should soak their feet for 15 min twice a day until the smell has improved and be warned that potassium permanganate stains the skin and everything else brown. Occasionally glutaraldehyde solutions are used instead, but allergy and yellow-stained skin are potential complications. Topical clindamycin is also effective.

**Iontophoresis.** This is the passage of a low-voltage direct current across the skin. Iontophoresis with tap water or with the anticholinergic drug glycopyronium bromide (glycopyrolate, USA) may help palmar or plantar hyperhidrosis. Patients attend two or three times a week for treatment until the condition improves. Repeated courses or maintenance therapy may be required.

![Fig. 12.16 Severe palmar hyperhidrosis demanding treatment.](image-url)
CHAPTER 12

**LEARNING POINT**

20% aluminium chloride hexahydrate in an alcohol base has now taken over from anticholinergic drugs and surgery for most patients with sweaty armpits and hands. Be sure the skin is dry before it is applied—use a hair-dryer if necessary.

*Botulinum toxin.* This binds to presynaptic nerve membranes and then inhibits the release of acetylcholine. It is now the treatment of choice for severe axillary or plantar hyperhidrosis, unresponsive to medical measures. Subdermal aliquots of the toxin are injected into the hyperhidrotic area of the axilla or sole, one region at a single session. Sweating is abolished after a delay of 2–3 days. Repeat injections (about every eighth month) are necessary as the sweating returns when the toxin has gone. Antibodies may form against the toxin and diminish its long-term effectiveness. Botulinum toxin is used less often for palmar hyperhidrosis because of the risk of paralysing the intrinsic muscles of the hand.

*Systemic treatment.* Oral anticholinergic agents such as Pro-Banthine and glycopyronium bromide (USA) are sometimes tried but their side-effects limit their value.

*Surgery.* This is used less nowadays as the above measures are usually effective. However, recalcitrant axillary hyperhidrosis can be treated by removing the vault of the axilla, which bears most of the sweat glands. These can be identified preoperatively by applying starch and iodine, which interact with sweat to colour the sweat gland openings blue. Thoracoscopic sympathetic trunkotomy (between the first and second thoracic ganglia) is effective for severe palmar hyperhidrosis alone but is a last resort.

**Hypohidrosis and anhidrosis**

*Anhidrosis caused by abnormality of the sweat glands*  

*Heat stroke.* Caused by sweat gland exhaustion, this is a medical emergency seen most often in elderly people moving to a hot climate. It can also occur in the young, during or after prolonged exercise, especially in hot climates. Patients present with hyperthermia, dry skin, weakness, headache, cramps and confusion, leading to vomiting, hypotension, oliguria, metabolic acidosis, hyperkalaemia, delirium and death. They should be cooled down immediately with cold water, and fluids and electrolytes must be replaced.

*Hypohidrotic ectodermal dysplasia.* This rare disorder is inherited as an X-linked recessive trait, in which the sweat glands are either absent or decreased. Affected boys have a characteristic facial appearance, with poor hair and teeth (Figs 13.13 and 13.14), and are intolerant of heat.

*Prematurity.* The sweat glands function poorly in premature babies nursed in incubators and hot nurseries.

*Anhidrosis caused by abnormalities of the nervous system*  

Anhidrosis may follow abnormalities anywhere in the sympathetic system, from the hypothalamus to the peripheral nerves. It can therefore be a feature of multiple sclerosis, a cerebral tumour, trauma, Horner’s syndrome or peripheral neuropathy (e.g. leprosy, alcoholic neuropathy and diabetes). Patients with widespread anhidrosis are heat-intolerant, developing nausea, dizziness, tachycardia and hyperthermia in hot surroundings.

*Anhidrosis or hypohidrosis caused by skin disease*  

Local hypohidrosis has been reported in many skin diseases, especially those that scar (e.g. lupus erythematosus and morphea). It may be a feature of Sjögren’s syndrome, ichthyosis, psoriasis and miliaria profunda (see below).

*Interference with sweat delivery*  

*Miliaria.* This is the result of plugging or rupture of sweat ducts. It occurs in hot humid climates, at any age, and is common in over-clothed infants in hot nurseries. The physical signs depend on where the ducts are blocked.
SEBACEOUS AND SWEAT GLAND DISORDERS

Notably not an immunodeficiency or a primary infection of the apocrine glands, although *Staphylococcus aureus*, anaerobic streptococci and *Bacterioides* spp. are frequently present. One group of workers has implicated *Streptococcus milleri* as the main pathogen. Treatment is unsatisfactory but should be as for acne vulgaris in the first instance. Systemic antibiotics help early lesions to resolve but are ineffective for chronic draining abscesses and sinuses. Incision and drainage of abscesses, and injections of intralesional triamcinolone (5–10 mg/mL) may reduce the incidence of deforming scars and sinus formation. Topical clindamycin has been shown to prevent new lesions from forming. Systemic antiandrogens help some women. Severe cases need plastic surgery to remove large areas of affected skin.

**Fox–Fordyce disease**

This rare disease of the apocrine ducts is comparable to miliaria rubra of the eccrine duct. It occurs in women after puberty. Itchy skin-coloured or light brown papules appear in the axillae and other areas where apocrine glands are found, such as the breasts and vulva. Treatment is not usually necessary but removal of the affected skin, or electrodessication of the most irritable lesions can be considered.

**Apocrine sweat glands**

Apocrine glands are limited to the axillae, nipples, peri-umbilical area, perineum and genitalia. The coiled tubular glands (larger than eccrine glands) lie deep in the dermis, and during sweating the luminal part of their cells is lost (decapitation secretion). Apocrine sweat passes via the duct into the midportion of the hair follicle. The action of bacteria on apocrine sweat is responsible for body odour. The glands are innervated by adrenergic fibres of the sympathetic nervous system.

**Suppurative hidradenitis (apocrine acne)**

This is a severe chronic suppurative disorder of the apocrine glands. Many papules, pustules, cysts, sinuses and scars occur in the axillae, groin and perianal areas. The condition may coexist with conglobate acne. Its cause is unknown, but an underlying follicular abnormality seems likely. Slightly raised androgen levels are found in some affected females. It is probably not an immunodeficiency or a primary infection of the apocrine glands, although *Staphylococcus aureus*, anaerobic streptococci and *Bacterioides* spp. are frequently present. One group of workers has implicated *Streptococcus milleri* as the main pathogen. Treatment is unsatisfactory but should be as for acne vulgaris in the first instance. Systemic antibiotics help early lesions to resolve but are ineffective for chronic draining abscesses and sinuses. Incision and drainage of abscesses, and injections of intralesional triamcinolone (5–10 mg/mL) may reduce the incidence of deforming scars and sinus formation. Topical clindamycin has been shown to prevent new lesions from forming. Systemic antiandrogens help some women. Severe cases need plastic surgery to remove large areas of affected skin.

**Further reading**

The hair

Hair is human plumage: we need just the right amount, in the right places. The twin torments of having too much or too little hair can be understood only when seen against the background of the formation and activity of normal hair follicles.

Hair follicles form before the ninth week of fetal life when the hair germ, a solid cylinder of cells, grows obliquely down into the dermis. Here it is met by a cluster of mesenchymal cells (the placode) bulging into the lower part of the hair germ to form the hair papilla. Eventually the papilla contains blood vessels bringing nutrients to the hair matrix. The sebaceous gland is an outgrowth at the side of the hair germ, establishing early the two parts of the pilosebaceous unit. The hair matrix, the germinative part of the follicle, is equivalent to the basal cells of the epidermis.

Melanocytes migrate into the matrix and are responsible for the different colours of hair (eumelanin, brown/black; phaeomelanin and trichochromes, red). Grey or white hair is caused by low pigment production, and the filling of the cells in the hair medulla with minute air bubbles that reflect light.

The structure of a typical hair follicle is shown in Fig. 13.1.

Classification

Hairs are classified into three main types.

1. **Lanugo hairs**. Fine long hairs covering the fetus, but shed about 1 month before birth.
2. **Vellus hairs**. Fine short unmedullated hairs covering much of the body surface. They replace the lanugo hairs just before birth.

![Fig. 13.1 Anatomy of the hair follicle.](image_url)
Regional Dermatology

looking at plucked hairs (a trichogram). On the scalp, about 85% are normally in anagen and 15% in the telogen phase. The length of hair is determined by the duration of anagen; e.g. the hairs of the eyebrows have shorter cycles than those of the scalp.

The hair cycle

Each follicle passes, independently of its neighbours, through regular cycles of growth and shedding. There are three phases of follicular activity (Fig. 13.2).

1. **Anagen.** The active phase of hair production.
2. **Catagen.** A short phase of conversion from active growth to the resting phase. Growth stops, and the end of the hair becomes club-shaped.
3. **Telogen.** A resting phase at the end of which the club hair is shed.

The duration of each of these stages varies from region to region. On the scalp (Fig. 13.3), said to contain an average of 100,000 hairs, anagen lasts for up to 5 years, catagen for about 2 weeks, and telogen for about 3 months. As many as 100 hairs may be shed from the normal scalp every day as a normal consequence of cycling. The proportion of hairs in the growing and resting stages can be estimated by looking at plucked hairs (a trichogram). On the scalp, about 85% are normally in anagen and 15% in the telogen phase. The length of hair is determined by the duration of anagen; e.g. the hairs of the eyebrows have shorter cycles than those of the scalp.

Each hair follicle goes through its growth cycles out of phase with its neighbours, so there is no moulting period. However, if many pass into the resting phase...
CHAPTER 13

Histologically, T lymphocytes cluster like a swarm of bees around affected hair bulbs, having been attracted and made to divide by cytokines from the dermal papilla. Alopecia areata is probably inherited as a complex genetic trait, with an increased occurrence in the first-degree relatives of affected subjects and twin concordance. The existence of trigger factors, such as stress, fits with this idea.

Presentation

A typical patch is uninflamed, with no scaling, but with easily seen empty hair follicles (Fig. 13.4). Pathognomonic ‘exclamation-mark’ hairs may be seen around the edge of enlarging areas. They are broken off about 4 mm from the scalp, and are narrowed and less pigmented proximally (Figs 13.5 and 13.6). Patches are most common in the scalp and beard but other areas, especially the eyelashes and eyebrows, can be affected too. An uncommon diffuse pattern is recognized, with exclamation-mark hairs scattered widely over a diffusely thinned scalp. Up to 50% of patients show fine pitting or wrinkling of the nails.

Course

The outcome is unpredictable. In a first attack, regrowth is usual within a few months. New hairs

<table>
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<tr>
<th>Table 13.1 Some causes of localized alopecia.</th>
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<td>Non-scarring</td>
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<tr>
<td>Alopecia areata</td>
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<tr>
<td>Androgenetic</td>
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<tr>
<td>Hair-pulling habit</td>
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<tr>
<td>Traction alopecia</td>
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<td>Scalp ringworm (human)</td>
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(telogen) at the same time, then a correspondingly large number will be shed 2–3 months later (see Telogen effluvium, below).

There are important racial differences in hair. Asians tend to have straight hair, Negroids woolly hair and Europeans wavy hair. These differences are associated with different cross-sectional shapes (round, flattened, etc.). Mongoloids have less facial and body hair than Mediterranean people who also have more hair than northern Europeans.

Alopecia

The term means loss of hair and alopecia has many causes and patterns. One convenient division is into localized and diffuse types. It is also important to decide whether or not the hair follicles have been replaced by scar tissue; if they have, regrowth cannot occur. The presence of any disease of the skin itself should also be noted.

Localized alopecia

Some of the most common types are listed in Table 13.1; only a few can be dealt with in detail.

Alopecia areata

This affects about 2% of the patients seen at our skin clinics.

Cause

An immunological basis is suspected because of an association with thyroid disease, vitiligo and atopy.
Involvement of the scalp margin (ophiasiform type), especially at the nape of the neck.

**Differential diagnosis**

Patches are not scaly, in contrast to ringworm, and are usually uninflamed, in contrast to lupus erythematosus and lichen planus. In the hair-pulling habit of children, and in traction alopecia, broken hairs may be seen but true exclamation-mark hairs are absent. Secondary syphilis can also cause a ‘moth-eaten’ patchy hair loss.

**Investigations**

None are usually needed. Syphilis can be excluded with serological tests if necessary. Organ-specific auto-antibody screens provide interesting information but do not affect management.

**Treatment**

A patient with a first or minor attack can be reassured about the prospects for regrowth. Tranquillizers may be helpful at the start. The use of systemic steroids should be avoided in most cases, but the intradermal injection of 0.2 mL of intralesional triamcinolone acetonide (10 mg/mL), raising a small bleb within an affected patch, leads to localized tufts of regrowth (Fig. 13.7) while not affecting the overall outcome. This may be useful to re-establish eyebrows or to stimulate hope. Spirit-based steroid lotions and mild irritants, such as 0.1–0.25% dithranol, are often used but with limited success. Ultraviolet radiation or even psoralen appear in the centre of patches as fine pale down, and gradually regain their normal thickness and colour, although the new hair may remain white in older patients. Subsequent episodes tend to be more extensive and regrowth is slower. Hair loss in some areas may coexist with regrowth in others. A few patients lose all the hair from their heads (alopecia totalis) or from the whole skin surface (alopecia universalis).

Regrowth is tiresomely erratic but the following suggest a poor prognosis.
1. Onset before puberty.
2. Association with atopy or Down’s syndrome.
3. Unusually widespread alopecia.

4. Involvement of the scalp margin (ophiasiform type), especially at the nape of the neck.

**Fig. 13.5** Exclamation-mark hairs: pathognomonic of alopecia areata.

**Fig. 13.6** An exclamation-mark hair.

**Fig. 13.7** Regrowth within a patch of alopecia areata after a triamcinolone injection.
However, in women the hair loss may be much more diffuse (Fig. 13.10), particularly over the crown. In bald areas, terminal hairs are replaced by finer vellus ones.

**Androgenetic alopecia (male-pattern baldness)**

**Cause**

Although clearly familial, the exact mode of inheritance has not yet been clarified. The idea of a single autosomal dominant gene, with reduced penetrance in women, now seems less likely than a polygenic type of inheritance. Male-pattern baldness is androgen-dependent; in females, androgenetic alopecia, with circulating levels of androgen within normal limits, is seen only in those who are strongly predisposed genetically.

**Presentation**

The common pattern in men (Fig. 13.9) is the loss of hair first from the temples, and then from the crown.

However, in women the hair loss may be much more diffuse (Fig. 13.10), particularly over the crown. In bald areas, terminal hairs are replaced by finer vellus ones.

**Clinical course**

Hair loss is relentless, tending to follow the family pattern with some losing hair quickly and others more slowly. The diffuse pattern seen in women tends to progress slowly.

**Complications**

Even minor hair loss may lead to great anxiety and rarely to a monosymptomatic hypochondriasis (p. 295). Bald scalps burn easily in the sun, and may develop multiple actinic keratoses. It has been suggested recently that bald men are more likely to have a heart attack than those with a full head of hair.
Traction alopecia

Cause
Hair can be pulled out by several procedures intended to beautify, including hot-combing to straighten kinky hair, tight hairstyles such as a pony tail or 'corn rows', and using hair rollers too often or too tightly.

Presentation
The changes are usually seen in girls and young women, particularly those whose hair has always tended to be thin anyway. The pattern of hair loss is determined by the cosmetic procedure in use, hair being lost where there is maximal tug. The term ‘marginal’ alopecia is applied to one common pattern in which hair loss is mainly around the edge of the scalp (at the sides or at the front (Fig. 13.11). The bald areas show short broken hairs, folliculitis and sometimes scarring.

Clinical course
Patients are often slow to accept that they are responsible for the hair loss, and notoriously slow to alter their cosmetic practices. Even if they do, regrowth is often disappointingly incomplete.

Differential diagnosis
The pattern of hair loss provides the main clue to the diagnosis and, if the possibility of traction alopecia

Trichotillomania
This is dealt with on p. 298.
Telogen effluvium

Cause

Telogen effluvium can be triggered by any severe illness, particularly those with bouts of fever or haemorrhage, by childbirth and by severe dieting. All of these synchronize catagen so that, later on, large numbers of hairs are lost at the same time.

Presentation and course

The diffuse hair fall, 2–3 months after the provoking illness, can be mild or severe. In the latter case Beau’s lines (p. 175) may be seen on the nails. Regrowth, not always complete, usually occurs within a few months.

Psoriasis

The rough removal of adherent scales can also remove hairs, but regrowth is the rule.

Scarring alopecia

Hair follicles can be damaged in many ways. If the follicular openings can no longer be seen with a lens, regrowth of hair cannot be expected.

Sometimes the cause is obvious: a severe burn, trauma, a carbuncle or an episode of inflammatory scalp ringworm. Discoid lupus erythematosus (p. 123), lichen planus (p. 64) and morphoea (p. 129) can also lead to scarring alopecia. The term ‘pseudopelade’ is applied to a slowly progressive non-inflamed type of scarring which leads to irregular areas of hair loss without any apparent preceding skin disease. If inflammation is present, a biopsy may help to establish the diagnosis.

Diffuse hair loss

Hair is lost evenly from the whole scalp; this may, or may not, be accompanied by a thinning visible to others (Fig. 13.12). Some of the most common causes are listed in Table 13.2, but often a simple explanation cannot be found.

Table 13.2 Some causes of diffuse hair loss.

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telogen effluvium</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>hypopituitarism</td>
</tr>
<tr>
<td>hypo- or hyperthyroidism</td>
</tr>
<tr>
<td>hypoparathyroidism</td>
</tr>
<tr>
<td>Drug-induced</td>
</tr>
<tr>
<td>antimitotic agents (anagen effluvium)</td>
</tr>
<tr>
<td>anticoagulants</td>
</tr>
<tr>
<td>vitamin A excess</td>
</tr>
<tr>
<td>oral contraceptives</td>
</tr>
<tr>
<td>Androgenetic</td>
</tr>
<tr>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Severe chronic illness</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Diffuse type of alopecia areata</td>
</tr>
</tbody>
</table>

Fig. 13.12 Diffuse hair loss causing much anxiety.

is kept in mind, there is usually no difficulty. The absence of exclamation-mark hairs distinguishes it from alopecia areata, and of scaling from tinea capitis.

Treatment

Patients have to stop doing whatever is causing their hair loss. Rollers that tug can be replaced by those that only heat.

Patchy hair loss caused by skin disease

Scalp ringworm

Inflammation, often with pustulation, is a feature of animal ringworm, and the resultant scarring can be severe. The classical scalp ringworm derived from human sources causes areas of scaling with broken hairs. The subject is covered in more detail on p. 216.
**Differential diagnosis**

This is from other types of diffuse hair loss (Table 13.2).

**Treatment**

This condition is unaffected by therapy, but patients can be reassured that their hair fall will be temporary.

**Other causes of diffuse hair loss**

The causes mentioned in Table 13.2 should be considered, and the exclamation-mark hairs of the diffuse type of alopecia areata should be looked for. If no cause is obvious, it is worth checking the haemoglobin, erythrocyte sedimentation rate (ESR), ANF, serum iron, thyroxine and thyroid-stimulating hormone (TSH) levels. Also consider checking the serum free testosterone and dihydroepiandrosterone sulphate levels in women with menstrual irregularities or hirsutism. However, it is true to say that often no cause for diffuse alopecia can be found.

**LEARNING POINTS**

1. Be sympathetic even if the hair loss seems trivial to you.
2. Reassure your patient that total baldness is not imminent.

**Rare genetic causes of hypotrichosis**

More than 300 genetic conditions exist that have hair abnormalities as one component. The hypohidrotic ectodermal dysplasias are a group of rare inherited disorders characterized by sparse hair, scanty sweat glands, and poor development of the nails and teeth. (Figs 13.13 and 13.14). Heat stroke may follow inadequate sweat production. One type is inherited as an X-linked recessive. The responsible gene for this type (on chromosome Xq12) has recently been shown to encode for a protein (ectodysplasin) involved in the regulation of ectodermal appendage formation. The genes responsible for the dominant/recessive types encode for the ectodysplasin receptor.

In other inherited disorders the hair may be beaded and brittle (*monilethrix*); flattened and twisted (*pili torti*); kinky (*Menkes’ syndrome* caused by mutations in a gene encoding for a copper transporting membrane protein); like bamboo (*Netherton’s syndrome*, caused by a gene on chromosome 5q32 encoding a serine protease inhibitor); partly broken in many places (*trichorrhexis nodosa*); ‘woolly’ or ‘uncombable’.
Hirsutism

Cause
Some degree of hirsutism may be a racial or familial trait, and minor facial hirsutism is common after the menopause. In addition, some patients without a family background of hirsutism become hirsute in the absence of any demonstrable hormonal cause (idiopathic hirsutism). Finally, some patients with hirsutism will have one of the disorders shown in Fig. 13.17.

Presentation
An excessive growth of hair appears in the beard area, on the chest and shoulder-tips, around the nipples and in the male pattern of pubic hair. Androgenetic alopecia may complete the picture.

Course
Familial, racial or idiopathic hirsutism tends to start at puberty and to worsen with age.

Complications
Virilization causes infertility; psychological disturbances are common.

Investigations
Significant hormonal abnormalities are not usually found in patients with a normal menstrual cycle.

Investigations are needed:
• if hirsutism occurs in childhood;
• if there are other features of virilization, such as clitoromegaly;
• if the hirsutism is of sudden or recent onset; or
• if there is menstrual irregularity or cessation.

The tests used will include measurement of the serum testosterone, sex-hormone-binding globulin, dehydroepiandrosterone sulphate, androstenedione and prolactin. Ovarian ultrasound is useful if polycystic ovaries are suspected.

Treatment (Fig. 13.17)
Any underlying disorder must be treated on its merits. Home remedies for minor hirsutism include commer-
treatment as it carries the risk of feminizing a male fetus. Spironolactone is used less often now.

Special depilatory creams (often containing a thioglycollate, p. 172), waxing or shaving, or making the appearance less obvious by bleaching; none remove the hair permanently. Plucking should probably be avoided as it can stimulate hair roots into anagen. The abnormally active follicles, if relatively few, can be destroyed by electrolysis. If the hairs are too numerous for this, the excess can be removed by laser (p. 326). Topical therapy with eflornithine, an inhibitor of ornithine decarboxylase, can slow regrowth. Oral antiandrogens (e.g. cyproterone acetate; Dianette, Formulary 2, p. 346) may sometimes be helpful, but will be needed long-term. Pregnancy must be avoided during such treatment as it carries the risk of feminizing a male fetus. Spironolactone is used less often now.

**LEARNING POINTS**

1. Full endocrinological assessment is needed for hirsutism plus virilization.
2. Significant hormonal abnormalities are rarely found in patients with a normal menstrual cycle.
Permanent waving solutions reduce disulphide bonds within hair keratin and so allow the hair to be deformed before being reset in a new position. The thioglycollates in use to dissolve disulphide bonds are also popular as chemical hair removers. If used incorrectly, either too strong or for too long, or on hair already damaged by excessive bleaching or waving, thioglycollate waving lotions can cause hairs to break off flush with the scalp. This hair loss, which can be severe although temporary, may be accompanied by an irritant dermatitis of the scalp.

The nails

The structure of the nail and nail bed is shown in Fig. 13.19. The hard keratin of the nail plate is formed in the nail matrix, which lies in an invagination of the epidermis (the nail fold) on the back of the terminal phalanx of each digit. The matrix runs from the proximal end of the floor of the nail fold to the distal margin of the lunule. From this area the nail plate grows forward over the nail bed, ending in a free margin at the tip of the digit. Longitudinal ridges and grooves on the under surface of the nail plate dovetail with similar ones on the upper surface of the nail bed. The nail bed is capable of producing small amounts of keratin which contribute to the nail and which are responsible for the ‘false nail’ formed when the nail matrix is obliterated by surgery or injury. The cuticle acts as a seal to protect the potential space of the nail fold from chemicals and from infection. The nails provide strength and protection for the terminal phalanx. Their presence helps with fine touch and with the handling of small objects.

Hypertrichosis

The localized type is most commonly seen over melanocytic naevi including Becker’s naevi (Fig. 13.18). It can also affect the sacral area—as a ‘satyr’s tuft’—in some patients with spina bifida. Excessive amounts of hair may grow near chronically inflamed joints or under plaster casts. Repeated shaving does not bring on hypertrichosis although occupational pressure may do so, e.g. from carrying weights on the shoulder.

Generalized hypertrichosis is much less common. Some causes are listed in Table 13.3.

Table 13.3 Some causes of generalized hypertrichosis.

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa, starvation</td>
</tr>
<tr>
<td>Drug-induced (minoxidil, diazoxide, cyclosporin)</td>
</tr>
<tr>
<td>Hepatic cutaneous porphyria (p. 287)</td>
</tr>
<tr>
<td>Fetal alcohol and fetal phenytoin syndromes</td>
</tr>
<tr>
<td>Hypertrichosis lanuginosa (both congenital type and acquired types are very rare—the latter signals an internal malignancy)</td>
</tr>
<tr>
<td>Some rare syndromes, e.g. Cornelia de Lange syndrome (hypertrichosis, microcephaly and mental deficiency) and Hurler’s syndrome</td>
</tr>
</tbody>
</table>

Fig. 13.18 A typical Becker’s naevus with marked localized hypertrichosis within a patch of hyperpigmentation.

Hair cosmetics

Hair can be made more attractive by dyeing, bleaching and waving, but there is often a price to be paid for beauty. Some hair dyes based on paraphenylenediamine are allergens (p. 78). Bleaches can weaken the hair shafts, and hair damaged in this way is especially susceptible to further damage by permanent waving.
Chronic trauma from sport and from ill-fitting shoes contributes to haemorrhage under the nails of the big toes, to the gross thickening of toenails known as onychogryphosis (Fig. 13.22), and to ingrowing nails. Onycholysis, a separation of the nail plate from the nail bed (Fig. 13.23), may be a result of minor trauma although it is also seen in nail psoriasis (Fig. 5.8), and possibly in thyroid disease. Usually no cause for it is

The rate at which nails grow varies from person to person: fingernails average between 0.5 and 1.2 mm per week, while toenails grow more slowly. Nails grow faster in the summer, if they are bitten, and in youth. They change with ageing from the thin, occasionally spooned nails of early childhood to the duller, paler and more opaque nails of the very old. Longitudinal ridging and beading are particularly common in the elderly.

Effects of trauma

Permanent ridges or splits in the nail plate can follow damage to the nail matrix. Splinter haemorrhages (Fig. 13.20), the linear nature of which is determined by longitudinal ridges and grooves in the nail bed, are most commonly seen under the nails of manual workers and are caused by minor trauma. They may also be a feature of psoriasis of the nail and of subacute bacterial endocarditis. Larger subungual haematomas (Fig. 13.21) are usually easy to identify but the trauma that caused them may have escaped notice and dark areas of altered blood can raise worries about the presence of a subungual melanoma.

Fig. 13.19 The nail and nail bed.

Fig. 13.20 Gross splinter haemorrhages caused by trauma.

Fig. 13.21 A subungual haematoma of the big toe. Although there was no history of trauma we were happy to watch this grow out over 6 months as the appearance was sudden, the colour was right and the nail folds showed no pigment.

Chronic trauma from sport and from ill-fitting shoes contributes to haemorrhage under the nails of the big toes, to the gross thickening of toenails known as onychogryphosis (Fig. 13.22), and to ingrowing nails. Onycholysis, a separation of the nail plate from the nail bed (Fig. 13.23), may be a result of minor trauma although it is also seen in nail psoriasis (Fig. 5.8), and possibly in thyroid disease. Usually no cause for it is

...
cuticles and the skin around the nails. Viral warts can be seeded rapidly in this way. In the common habit tic nail dystrophy, the cuticle of the thumbnail is the target for picking or rubbing. This repetitive trauma causes a ladder pattern of transverse ridges and grooves to run up the centre of the nail plate (Fig. 13.23).

Lamellar splitting of the distal part of the fingernails, so commonly seen in housewives, has been attributed to repeated wetting and drying (Fig. 13.23).

Attempts to beautify nails can lead to contact allergy. Culprits include the acrylate adhesive used with artificial nails and formaldehyde in nail hardeners. In contrast, contact dermatitis caused by allergens in nail polish itself seldom affects the fingers but presents as small itchy eczematous areas where the nail plates rest against the skin during sleep. The eyelids, face and neck are favourite sites.

The nail in systemic disease

The nails can provide useful clues for general physicians.

Fig. 13.22 Onychogryphosis.

found. The space created may be colonized by yeasts, or by bacteria such as *Pseudomonas aeruginosa*, which turns it an ugly green colour.

Some nervous habits damage the nails. Bitten nails are short and irregular; some people also bite their

Fig. 13.23 Some nail plate abnormalities.

The greatly thickened nail of pachyonychia congenita

The short wide nail of nail ‘*en racquette*’

Habit tic nail dystrophy. A ladder pattern of transverse ridges and furrows runs up the centre of a thumb nail

Nail being elevated and distorted by a subungual exostosis

Onycholysis is the separation of the nail plate from the nail bed (Fig. 5.8)

Lamellar splitting – flaking and fragility of the distal end of the nail plate
**Koilonychia**, a spooning and thinning of the nail plate, indicates iron deficiency (Fig. 13.26).

**Colour changes**: the ‘half-and-half’ nail, with a white proximal and red or brown distal half, is seen in a minority of patients with chronic renal failure. Whitening of the nail plates may be related to hypoalbuminaemia, as in cirrhosis of the liver. Some drugs, notably antimalarials, antibiotics and phenothiazines, can discolor the nails.

**Beau’s lines** are transverse grooves which appear synchronously on all nails a few weeks after an acute illness, and which grow steadily out to the free margin (Fig. 13.26).

**Connective tissue disorders**: nail fold telangiectasia or erythema is a useful physical sign in dermatomyositis, systemic sclerosis and systemic lupus erythematosus (Fig. 13.27). In dermatomyositis the cuticles become shaggy, and in systemic sclerosis loss of finger pulp leads to overcurvature of the nail plates. Thin nails, with longitudinal ridging and sometimes partial onycholysis, are seen when the peripheral circulation is impaired, as in Raynaud’s phenomenon.

**Nail changes in the common dermatoses**

**Psoriasis**

Most patients with psoriasis have nail changes at some stage; severe nail involvement is more likely in the presence of arthritis. The best-known nail change is pitting of the surface of the nail plate (Fig. 5.7). Almost as common is psoriasis under the nail plate, showing up as red or brown areas, often with onycholysis bordered by obvious discoloration (Fig. 5.8). There is no effective treatment for psoriasis of the nails.

**Eczema**

Some patients with itchy chronic eczema bring their nails to a high state of polish by scratching. In addition, eczema of the nail folds may lead to a coarse irregularity with transverse ridging of the adjacent nail plates.

**Lichen planus**

Some 10% of patients with lichen planus have nail changes. Most often this is a reversible thinning of the
The concave, spoon-shaped nail of koilonychia (seen in iron deficiency)

Beau’s line: a transverse furrow, across all nails, due to slow growth during a severe illness

Telangiectatic or thrombosed capillaries in the proximal nail fold are an important pointer towards connective tissue disease (Fig. 13.27)

Pterygium – the cuticle is adherent to the nail plate and grows out with it. Seen in lichen planus

In chronic paronychia, pus exudes from below the bolstered, swollen nail folds. The adjacent nail becomes ridged and discoloured (Fig. 13.28)

In a dermatophyte infection the discolouration and crumbliness start at the free margin and spread proximally (Fig. 13.40)

Alopecia areata

The more severe the hair loss, the more likely there is to be nail involvement. A roughness or fine pitting is seen on the surface of the nail plates and the lunulae may appear mottled.
Infections

Acute paronychia

The portal of entry for the organisms concerned, usually staphylococci, is a break in the skin or cuticle as a result of minor trauma. The subsequent acute inflammation, often with the formation of pus in the nail fold or under the nail, requires systemic treatment with flucloxacillin or erythromycin (Formulary 2, p. 341) and appropriate surgical drainage.

Chronic paronychia

Cause

A combination of circumstances can allow a mixture of opportunistic pathogens (yeasts, Gram-positive cocci and Gram-negative rods) to colonize the space between the nail fold and nail plate. Predisposing factors include a poor peripheral circulation, wet work, working with flour, diabetes, vaginal candidosis and overvigorous cutting back of the cuticles.

Presentation and course

The nail folds become tender and swollen (Figs 13.26 and 13.28) and small amounts of pus are discharged at intervals. The cuticular seal is damaged and the adjacent nail plate becomes ridged and discoloured. The condition may last for years.

Differential diagnosis

In atypical cases, consider the outside chance of an amelanotic melanoma. Paronychia should not be confused with a dermatophyte infection in which the nail folds are not primarily affected.

Fig. 13.28 Paronychia with secondary nail ridging.

Investigations

Test the urine for sugar, check for vaginal candidosis. Pus should be cultured.

Treatment

Manicuring of the cuticle should cease. The hands should be kept as warm and as dry as possible, and the damaged nail folds packed several times a day with an imidazole cream (Formulary 1, p. 335). If there is no response, and swabs confirm that candida is present, a 2-week course of itraconazole should be considered (Formulary 2, p. 343).

Dermatophyte infections (Figs 13.26 and 14.40)

Cause

The common dermatophytes that cause tinea pedis can also invade the nails (p. 215).

Presentation

Toenail infection is common and associated with tinea pedis. The early changes occur at the free edge of the nail and spread proximally. The nail plate becomes yellow, crumbly and thickened. Usually only a few nails are infected but occasionally all are. The fingernails are involved less often and the changes, in contrast to those of psoriasis, are usually confined to one hand.
Clinical course
The condition seldom clears spontaneously.

Differential diagnosis
Psoriasis has been mentioned. Yeast infections of the nail plate, much more rare than dermatophyte infections, can look similar. Coexisting tinea pedis favours dermatophyte infection of the nail.

Investigations
Microscopic examination of a nail clipping is a simple procedure (p. 35). Cultures should be carried out in a mycology laboratory.

Treatment
This is given on p. 217. Remember that most symptom-free fungal infections of the toenails need no treatment at all.

Tumours
Peri-ungual warts are common and stubborn. Cryotherapy must be used carefully to avoid damage to the nail matrix. It is painful but effective.

Peri-ungual fibromas (see Fig. 21.5) arise from the nail folds, usually in late childhood, in patients with tuberous sclerosis.

Glomus tumours can occur beneath the nail plate. The small red or bluish lesions are exquisitely painful if touched and when the temperature changes. Treatment is surgical.

Subungual exostoses (Fig. 13.22) protrude painfully under the nail plate. Usually secondary to trauma to the terminal phalanx, the bony abnormality can be seen on X-ray and treatment is surgical.

Myxoid cysts (Fig. 13.29) occur on the proximal nail folds, usually of the fingers. The smooth domed swelling contains a clear jelly-like material that transilluminates well. A groove may form on the adjacent nail plate. Cryotherapy, injections of triamcinolone and surgical excision all have their advocates.

Malignant melanoma should be suspected in any subungual pigmented lesion, particularly if the pigment spreads to the surrounding skin. Subungual haematomas may cause confusion but ‘grow out’ with the nail (Fig. 13.21). The risk of misdiagnosis is highest with an amelanotic melanoma, which may mimic chronic paronychia or a pyogenic granuloma.

Some other nail abnormalities
A few people are born with one or more nails missing. In addition there are many conditions, either inherited or associated with chromosomal abnormalities and usually rare, in which nail changes form a minor part of the clinical picture. Most cannot be dealt with here.

In the rare nail–patella syndrome, the thumbnails, and to a lesser extent those of the fingers, are smaller than normal. Rudimentary patellae, and renal disease iliac spines complete the syndrome, which is inherited as an autosomal dominant trait linked with the locus controlling ABO blood groups.

Pachyonychia congenita is also rare and inherited as an autosomal dominant trait. The nails are grossly thickened, especially peripherally, and have a curious triangular profile (Fig. 13.22). Hyperkeratosis may occur on areas of friction on the legs and feet.

permanent loss of the nails may be seen with the dystrophic types of epidermolysis bullosa (p. 117).

In the yellow nail syndrome (Fig. 13.30) the nail changes begin in adult life, against a background of
Lichen planus

Cause
The cause of oral lichen planus is unknown (see also Chapter 6). However, some 40% of patients with symptomatic lichen planus of the mouth have relevant allergies, diagnosable by patch testing. These are usually to metals (especially gold and mercury) and flavourings such as cinnamon, peppermint and spearmint. Lichen planus also results from drug reactions, liver disease and bone marrow transplantation.

Presentation
When a lichen planus-like cutaneous eruption is present, finding lichen planus in the mouth confirms the diagnosis, and vice versa. In the mouth, typically, there is a lace-like whitening of the buccal mucosae (Fig. 6.4), but sometimes this laciness is not present. Oral lichen planus can also be red, and can ulcerate. A ‘desquamative gingivitis’ may occur, in which the mucosa shears off with friction, such as that from brushing the teeth or eating an apple. Desquamative gingivitis can also result from pemphigus or pemphigoid (see below). Often oral lichen planus is asymptomatic and more of a curiosity than a problem for the patient.

Course
Oral lichen planus can last for years—even for a lifetime. Asymptomatic lichen planus does not usually progress to the symptomatic form.

Differential diagnosis
In its classic lace-like state, the appearance of oral lichen planus and candida infections, from the dysplastic ones that are the precursors of carcinoma.

Some skin diseases cause ulceration in the mouth. These ulcers are accompanied by skin diseases elsewhere on the body, and making a diagnosis there is easier than in the mouth. In other patients with mouth ulcers, the course of the ulcers or erosions, and their size and location in the mouth, provide diagnostic clues. Table 13.4 lists some common tongue troubles.

Fig. 13.30 The curved slow-growing greenish-yellow nails of the yellow nail syndrome.
Investigations

A potassium hydroxide (KOH) examination and a culture will rule out candidasis. Biopsy will determine if a white patch is dysplastic or not. The histology of lichen planus, as seen in the skin, may be less typical in planus is diagnostic. Dysplastic leukoplakias are more likely to be focal, appearing on only a portion of the mucosae, gingivae or lips. They are also more likely to be red and symptomatic, and shown by those who have smoked cigarettes or chewed tobacco. Candida albicans infections may occasionally be considered, but their white patches scrape off.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furred tongue</td>
<td>Hypertrophy of the filiform papillae</td>
<td>Brush the tongue</td>
</tr>
<tr>
<td>Black hairy tongue (Fig. 13.31)</td>
<td>Pigmentation and hypertrophy of filiform papillae caused due to bacterial overgrowth</td>
<td>Brush the tongue</td>
</tr>
<tr>
<td>Smooth tongue</td>
<td>Nutritional deficiency, sprue, malabsorption</td>
<td>Vitamins, nutrition</td>
</tr>
<tr>
<td>Fissured tongue</td>
<td>Congenital, Down's syndrome, ageing changes</td>
<td>No treatment needed</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
<td>Developmental defect and candidosis. Smoking and dentures worsen</td>
<td>No treatment needed</td>
</tr>
<tr>
<td>Geographic tongue (Fig. 13.32)</td>
<td>Familial, atopic, psoriasis</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>Varices</td>
<td>Blue compressible blebs of veins</td>
<td>No treatment needed</td>
</tr>
<tr>
<td>Hairy leukoplakia (Fig. 14.36)</td>
<td>Epstein–Barr virus infection in patients with HIV/AIDS</td>
<td>Highly active retroviral therapies (HAART)</td>
</tr>
<tr>
<td>Herpetic glossitis</td>
<td>Painful fissures without vesicles</td>
<td>Aciclovir group (p. 344)</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>Developmental, tumours, infections, amyloidosis, thyroid</td>
<td>Treat the cause</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>Trauma, candida, menopause, diabetes, nutritional, dry mouth</td>
<td>Treat the cause, use tricyclic antidepressants</td>
</tr>
</tbody>
</table>

Fig. 13.31  Black hairy tongue.

Fig. 13.32  Geographic tongue.

Table 13.4  Some common tongue problems.
the mouth, and may even suggest a dermatitis. Patch testing may be useful as allergic causes can be cured by allergen elimination. Liver function tests, and tests for hepatitis B, hepatitis C and antimitochondrial antibodies, are often recommended.

Treatment

If asymptomatic, no treatment is necessary. High potency topical steroids, in gel or ointment bases, are worth a try if the lesions are painful or ulcerated. Failing that, a few patients require oral prednisone; they should be referred to a dermatologist or specialist in oral medicine. Topical tacrolimus ointment may help, but treatment with this new agent is experimental.

Complications

Watch out for carcinoma, even if previous biopsies have shown no dysplasia. The risk is highest in the ulcerative forms, and the overall risk for development of squamous cell carcinoma in oral lichen planus is probably 1–5%. It should be suspected if an area becomes thickened, nodular or ulcerates.

Candidiasis

Cause and presentation

Infections with Candida albicans appear suddenly, on the tongue, lips or other mucosae, in the ‘pseudomembranous form’ (also called thrush; Fig. 14.47). Small lesions are more common than large ones. About 15% of infants get thrush on the tongue, lips or buccal mucosa, often from an infection acquired while passing through the birth canal. Sometimes candidiasis appears as red sore patches under dentures, or as angular cheilitis (perlèche).

Course

If the candidiasis is a complication of systemic antibiotic therapy, treatment will be curative. Immunosuppressed and denture-wearing patients often have recurrent disease.

Differential diagnosis

Many tongues are coated with desquamated epithelial cells that create a yellow wet powder on their surface. This scapes off easily, and shows no inflammation underneath. Lichen planus, oral hairy leukoplakia and dysplastic leukoplakia may cause confusion.

Investigations

Thrush does not normally occur in healthy adults, in whom the appearance of candidiasis needs more investigation than just a simple diagnosis by appearance, KOH examination or culture. Table 13.5 lists some possible underlying causes.

Treatment

Topical and systemic imidazoles are the treatments of choice. Creams and solutions can be used, but sucking on a clotrimazole troche (Formulary 1, p. 335) three times daily is better. Some patients are best treated with fluconazole, 150 mg once daily for 1–3 days. If an underlying condition is present, this should be identified and treated. Patients with ‘denture sore mouth’ should scrub their dentures each night with toothpaste and a toothbrush, sleep without dentures, and swish a teaspoonful of nystatin solution around the dentureless mouth three times a day.

Table 13.5 Some possible causes underlying oral candidiasis in adults.

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic treatment</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Myelodysplastic syndromes</td>
</tr>
<tr>
<td>leukaemia</td>
</tr>
<tr>
<td>lymphoma</td>
</tr>
<tr>
<td>thymoma</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Inhalation of corticosteroids for asthma</td>
</tr>
<tr>
<td>Widespread metastatic malignancy</td>
</tr>
<tr>
<td>Vitamin deficiency</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Xerostomia</td>
</tr>
<tr>
<td>Previous radiation therapy to mouth</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Dentures</td>
</tr>
<tr>
<td>Chronic mucocutaneous candidiasis (on skin and nails too; p. 219)</td>
</tr>
</tbody>
</table>

...
Contact stomatitis

This underdiagnosed problem usually causes a transient soreness, associated with a diffuse redness of the lips and buccal gingivae. Mouthwashes, hard sweets (candies) and hot pizzas are common causes of the irritant type, whereas cinnamon, vanilla, peppermint, spearmint and dentifrices are the most common causes of allergic contact stomatitis. When local stomatitis or ulcers occur near a gold tooth filling, gold allergy should be suspected, but patch testing is needed before recommending that the filling should be removed.

Ulcers

One problem with oral ulcers (as with ulcers elsewhere) is the usual lack of a primary lesion, such as a bulla, papule or plaque. Ulcers are often secondary reactions which rob the clinician of the chance to make a morphological diagnosis. The history, the location of the ulcers within the mouth, their duration and the presence of coexisting non-oral signs or symptoms, especially of the skin, are then all-important clues to the underlying diagnosis.

Bullous diseases

Pemphigus and pemphigoid are most likely (see also Chapter 9).

Pemphigus causes large painful long-lasting erosions (Fig. 9.3). The whole mouth can be involved, but more often it affects just the lips and buccal mucosa. Desquamative gingivitis can occur. The ulcers are large, appear without warning and last months. A biopsy may show an intraepithelial acantholysis and should not be taken from an ulcer, but from normal-appearing mucosa in an active area. Direct immunofluorescence (biopsy normal mucosa) shows antibody rimming each keratinocyte.

Cicatricial (scarring) pemphigoid affects the mucous membranes predominantly, but occasionally affects the skin too. The eyelid conjunctiva and other mucosae can also be affected; scarring often results (see Fig. 9.8). Cicatricial pemphigoid is also a cause of desquamative gingivitis. Biopsy shows a subepidermal bulla, and direct immunofluorescence a linear band of IgG and C3 at the dermal–mucosal junction.

Aphthae

Presentation

These common small oval painful mouth ulcers arise, usually without an obvious cause, most often in ‘movable mucosae’ such as the gutters of the mouth, tongue or cheek (Fig. 13.33). An area of tenderness changes into a small red papule that quickly turns into a grey 2–5 mm painful ulcer with a red areola. Herpetiform aphthae occur in groups of 2–5 tiny painful ulcers. Major aphthae (periadenitis mucosa necrotica) are usually larger than 1 cm across and tend to appear in the back of the mouth.

Course

Small ulcers heal in a week or two; the pain stops within days. Major aphthae may persist for months.

Differential diagnosis

Recurrent herpes simplex infections mimic herpetiform aphthae but, in the latter, cultures are negative and blisters are not seen. Behçet’s disease causes confusion in patients with major aphthae. In fact, a diagnosis of Behçet’s is often wrongly made in patients with recurrent aphthae of all sorts, when the patient has some other skin disease or joint pain. Patients with true Behçet’s disease should have at least two of these other findings: genital ulcers, pustular vasculitis of skin, synovitis, uveitis or meningoencephalitis.
Telangiectases may suggest hereditary haemorrhagic telangiectasia. These patients may also have telangiectases in their intestinal tract leading to gastrointestinal bleeding, and arteriovenous fistulae especially in the lungs that may lead to cerebral embolism.

Venous lakes are blue or black papules on the lips (Fig. 13.35). These melanoma-like lesions worry patients and doctors alike, but pressure with a diascopy or glass slide causes them to blanch.

Multiple, somewhat translucent, papules may suggest Cowden’s syndrome. These are fibromas. Patients with Cowden’s syndrome have facial papules and nodules (tricholemmomas and fibromas), fibrocystic disease of the breasts and a great propensity to develop malignant tumours of the breast, thyroid and other organs.

Patients with the multiple mucosal neuroma syndrome have neuromas in their mouths, and 75% of those with this autosomal dominantly inherited disorder also have medulary carcinoma of the thyroid. Many also develop pheochromocytomas. Many small bumps appear along the lips, tongue and buccal mucosae.

Pyogenic granulomas of the gingiva appear as quick-growing red bleeding papules. They are reactive proliferations of blood vessels, and often develop in pregnancy (‘pregnancy tumours’).

Fibromas may result from dentures, or from resolving or indolent pyogenic granulomas, but can also appear without reason, usually on the gingiva of adults. Tooth bites may cause fibromas to appear on the tongue and on the buccal mucosae. Cowden’s disease (see above) should be considered if multiple lesions are present.

Warts in the mouth are not uncommon.

Investigations

Usually none are needed. Occasional associations include Crohn’s disease, ulcerative colitis, gluten-sensitive enteropathy, cyclical neutropenia, other neutropenias, HIV infection, and deficiencies of iron, vitamin B₁₂ or folate.

Treatment

Prevention is best. Trauma, such as aggressive tooth brushing, hard or aggravating foods and stress should be avoided if relevant. The application of a topical corticosteroid gel, such as fluocinonide, to new lesions may shorten their course. In severe or complex cases, consider referral.

Some other oral lumps, bumps and colour changes

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- Warts in the mouth are not uncommon.
grow, and squamous cell carcinomas of the mouth are no exception. Plaques and hard areas may ulcerate.

Differential diagnosis

Confusion occurs with ulcerative lichen planus and other causes of white and red patches. Biopsy will differentiate a squamous cell carcinoma from these other conditions.

Treatment

Dermatologists often treat lip cancers by a wedge excision through all layers of the lip, with primary repair. Oral surgeons or otolaryngologists usually remove intraoral cancers. Metastatic disease may require radiotherapy or chemotherapy.

Complications

Squamous cell carcinomas of the lip caused by sun exposure carry a much better prognosis than the others. Left untreated, squamous cell carcinomas are prone to metastasize to regional lymph nodes and elsewhere. The overall 5-year survival for intraoral squamous cell carcinoma is about 40–50%.

The genitals

The genital area is richly supplied with cutaneous nerves. This means that skin disease there makes life more miserable than might be expected from its extent or apparent severity. In addition, patients often feel a special shame when their genitals harbour skin
transplanted into affected areas, but the disease goes away when the grafted skin is returned to a distant site.

**Presentation**

The affected areas on the vulva, penis (Fig. 13.38), perineum and/or perianal skin show well-marginated white thin fragile patches with a crinkled surface. Itching can be severe, especially in women. The fragility of the atrophic areas may lead to purpura and erosions. Scratching can cause lichenification, and diagnostic confusion.

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**Table 13.6** Some benign genital problems.

<table>
<thead>
<tr>
<th>Pearly penile papules</th>
<th>Pinhead-sized angiofibromas of the glans penis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fordyce spots</td>
<td>Ectopic sebaceous glands of the glans penis</td>
</tr>
<tr>
<td>Angiokeratomas</td>
<td>Black papules of scrotum</td>
</tr>
<tr>
<td>Balanitis</td>
<td>Many types, but poor hygiene is common</td>
</tr>
<tr>
<td>Warts (condyloma acumina)</td>
<td>Cauliflower-like growths of moist genital skin (see Chapter 14)</td>
</tr>
<tr>
<td>Fixed drug eruptions</td>
<td>Red plaques or ulcers can be localized to the penis (see Chapter 22)</td>
</tr>
<tr>
<td>Lichen planus (Fig. 13.37)</td>
<td>Look for lesions in the mouth or on the skin to confirm the diagnosis</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Often favours the glans penis</td>
</tr>
<tr>
<td>Paget’s disease</td>
<td>Intraepithelial adenocarcinoma appearing as a margined red plaque</td>
</tr>
<tr>
<td>Infections</td>
<td>Syphilis, herpes simplex, chancroid, lymphogranuloma venereum</td>
</tr>
</tbody>
</table>

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**Benign conditions**

An array of problems can plague the genitals; Table 13.6 lists some of them.

**Vulvovaginitis**

Inflammatory diseases of the vagina often also affect the vulva, but the vagina alone can be affected. Vaginitis causes discharge, odour, painful intercourse and itching or burning sensations. The differential diagnosis includes candidiasis, trichomoniasis, bacterial vaginosis, cytolytic vaginosis and atrophic vaginitis. The diagnosis can be made by the appearance of the discharge both grossly and under the microscope. Most patients with vaginitis get their care from gynaecologists. Swabs for microbiological examination are essential.

**Lichen sclerosus** (see also Chapter 10)

**Cause**

This is unknown but local conditions have a role: not only does skin develop the disease after being
damage, and the papillary dermis contains a homogeneous pink-staining material and lymphocytes.

Treatment
At first sight it might seem unwise to rub potent topical steroids onto atrophic thin occluded skin. Yet, treatment with potent topical steroids not only reduces itch, pain and misery, but also reverses hypopigmentation and atrophy by shutting down its cause. However, atrophy, striae and other complications can develop on untreated adjacent skin, if the medication spreads there. Ointments are preferable to creams. Only small amounts (15 g) should be dispensed. After a course of 8–12 weeks, weaker topical steroids can be used to maintain a remission.

Complications
As mentioned earlier, scarring can destroy anatomical structures and narrow the vaginal opening. Squamous cell carcinomas may develop in men as well as women. Any focal thickening needs a biopsy.

Vulval and scrotal pruritus

Cause
Itching of the genital skin is usually caused by skin disease, or by rubbing, sweating, irritation or occlusion. Once started, genital itching seems able to continue on its own.

Presentation
The vulva and scrotum contain nerves that normally transmit pleasurable sensations. However, itching itself is not pleasurable, although scratching is. A torturing itch may be present all day, but more frequently appears or worsens at night. Once scratching has started, it perpetuates itself. The history is of an incessant and embarrassed scratching. Examination may show normal skin, or the tell-tale signs of excoriations and lichenification.

Differential diagnosis
The sharply marginated white patches of vitiligo can afflict the vulva and penis but lack atrophy, and typical vitiligo may be found elsewhere on the body. Neurodermatitis may be superimposed upon lichen sclerosus after incessant scratching.

Investigations
Biopsy is often unnecessary but the appearances are distinctive. The epidermis is thin, the basal layer shows

Women are more commonly afflicted than men, but pre-adolescent girls and boys also can develop this problem. In girls, the white patches circling the vulva and anus take on an hourglass shape around the orifices.

Course
As time goes on, scarring occurs. In adult women, the clitoral prepuce may scar over the clitoris, and the vaginal introitus may narrow, preventing enjoyable sexual intercourse. Scarring is rare in girls and boys; treatment may prevent it occurring in adults.

Differential diagnosis
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Fig. 13.38 Lichen sclerosus of the foreskin, carrying the risk of causing phimosis.
Malignant conditions

Squamous cell carcinoma

Cause

Human papilloma viruses, especially HPV types 6, 11, 16 and 18, often play a part. These are sexually transmitted, so the risk of carcinoma of the vulva or penis is greatest in those who have had many sexual partners. Squamous cell carcinoma of the glans penis is especially common in the uncircumcised. Smegma can incite inflammation leading to both phimosis and carcinoma. Exposure to tar also predisposes to scrotal carcinoma. Other predisposing factors are immunosuppression, lichen sclerosus and, possibly, lichen planus. Cancer can also develop from Bowenoid papulosis—a growths on the penis that resemble dark seborrhoeic keratoses clinically, and Bowen’s disease histologically. The female equivalent is vulvar intraepithelial neoplasia.

Presentation

In men, a glistening irregular red moist patch (Fig. 13.39; Bowen’s disease/erythroplasia of Queyrat) develops on an uncircumcised penis, either on the glans or on

Table 13.7 Nine common groin dermatoses.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea cruris</td>
<td>Involves the groin but seldom the scrotum</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Beefy red with satellite papules and pustules</td>
</tr>
<tr>
<td>Erythrasma</td>
<td>Brown patches of the upper thighs</td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>Burning sensations may predominate</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>The scrotum may be oedematous</td>
</tr>
<tr>
<td>Inverse psoriasis</td>
<td>Beefy red margined plaques extend up the gluteal</td>
</tr>
<tr>
<td>Seborrhoedic dermatitis</td>
<td>Look at the scalp for disease there, to confirm</td>
</tr>
<tr>
<td>Neurodermatitis</td>
<td>It feels wonderful to scratch an itchy groin</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>Skin breaks down from maceration</td>
</tr>
</tbody>
</table>
the inner prepuce. Maceration may make it look white until evaporation reveals its true colour. It enlarges slowly, and invasion and tumour formation may not occur for years in immunocompetent men. In women, the precursor lesion is often Bowen’s disease presenting as a sharply margined, very slowly growing, mildly hyperkeratotic or slightly scaling, oddly shaped red patch or plaque that is usually a single lesion on one labia or in the perineum. This may become huge (up to 10 cm diameter). Sometimes cancer of the penis or labia resembles a large wart destroying the underlying tissue. Biopsy confirms the diagnosis.

Course

Eventually the precursor lesions become frankly invasive and capable of metastasizing. Invasive carcinomas present either as bleeding ulcerated indurated plaques, or as tumorous nodules.

Treatment

Mohs’ micrographic excision (p. 323) is probably the best treatment for small and minimally invasive carcinomas, but partial penectomy is indicated if the tumour is large. Precursor lesions such as warts, Bowenoid papulosis, vulvar intraepithelial neoplasia and Bowen’s disease can be destroyed with laser surgery (p. 326) or cryotherapy (p. 324). In some patients, topical applications of the cytokine-inducer imiquimod cream or the chemotherapeutic 5-fluorouracil cream can be curative.

Fig. 13.39 Erythroplasia of Queyrat.

Further reading

Bacterial infections

The resident flora of the skin

The surface of the skin teems with micro-organisms, which are most numerous in moist hairy areas, rich in sebaceous glands. Organisms are found, in clusters, in irregularities in the stratum corneum and within the hair follicles. The resident flora is a mixture of harmless and poorly classified staphylococci, micrococci and diphtheroids. *Staphylococcus epidermidis* and aerobic diphtheroids predominate on the surface, and anaerobic diphtheroids (propionibacteria sp.) deep in the hair follicles. Several species of lipophilic yeasts also exist on the skin. The proportion of the different organisms varies from person to person but, once established, an individual’s skin flora tends to remain stable and helps to defend the skin against outside pathogens by bacterial interference or anti-biotic production. Nevertheless, overgrowth of skin diphtheroids can itself lead to clinical problems. The role of Propionibacteria in the pathogenesis of acne is discussed on p. 149. Overgrowth of aerobic diphtheroids causes the following conditions.

**Trichomycosis axillaris**

This is a common condition, seen, if looked for, in up to one-quarter of adult males. The axillary hairs become beaded with concretions, usually yellow, made up of colonies of commensal diphtheroids. Clothing becomes stained in the armpits. Topical antibiotic ointments, or shaving, will clear the condition.

**Pitted keratolysis**

The combination of unusually sweaty feet and occlusive shoes encourages the growth of diphtheroid organisms that can digest keratin. The result is a cribriform pattern of fine punched-out depressions on the plantar surface (Fig. 14.1), coupled with an unpleasant smell (of methane-thiol). Fusidic acid or mupirocin ointment is usually effective. Occlusive footwear should be replaced by sandals and cotton socks if possible.

**Erythrasma**

Some diphtheroid members of the skin flora produce porphyrins when grown in a suitable medium; as a result their colonies fluoresce coral pink under Wood’s light. Overgrowth of these strains is sometimes the cause of symptom-free macular wrinkled slightly scaly pink, brown or macerated white areas, most often found in the armpits or groins, or between the toes. In diabetics, larger areas of the trunk may be involved. Diagnosis is helped by the fact that these areas also fluoresce coral pink with Wood’s light. Topical fusidic acid or miconazole will clear the condition.
Staphylococcal infections

*Staphylococcus aureus* is not part of the resident flora of the skin other than in a minority who carry it in their nostrils, perineum or armpits. Carriage rates vary with age. Nasal carriage is almost invariable in babies born in hospital, becomes less frequent during infancy, and rises again during the school years to the adult level of roughly 30%. Rather fewer carry the organism in the armpits or groin. Staphylococci can also multiply on areas of diseased skin such as eczema, often without causing obvious sepsis. A minor breach in the skin’s defences is probably necessary for a frank staphylococcal infection to establish itself; some strains are particularly likely to cause skin sepsis.

Impetigo

*Cause*

Impetigo may be caused by staphylococci, streptococci, or by both together. As a useful rule of thumb, the bullous type is usually caused by *Staphylococcus aureus*, whereas the crusted ulcerated type is caused by β-haemolytic strains of streptococci. Both are highly contagious.

*Presentation*

A thin-walled flaccid clear blister forms, and may become pustular before rupturing to leave an extending area of exudation and yellowish crusting (Fig. 14.2). Lesions are often multiple, particularly around the face. The lesions may be more obviously bullous in infants. A follicular type of impetigo (superficial folliculitis) is also common.

*Course*

The condition can spread rapidly through a family or class. It tends to clear slowly even without treatment.

*Complications*

Streptococcal impetigo can trigger an acute glomerulonephritis.

Fig. 14.2 Impetigo on an uncommon site showing erosions, crusting and rupture blisters.

Differential diagnosis

Herpes simplex may become impetiginized, as may eczema. Always think of a possible underlying cause such as this. Recurrent impetigo of the head and neck, for example, should prompt a search for scalp lice.

Investigation and treatment

The diagnosis is usually made on clinical grounds. Swabs should be taken and sent to the laboratory for culture, but treatment must not be held up until the results are available. Systemic antibiotics (such as flucloxacillin, erythromycin or cephalexin (cefoxitin)) are needed for severe cases or if a nephritogenic strain of streptococcus is suspected (penicillin V). For minor cases the removal of crusts and a topical antibiotic such as neomycin, fusidic acid (not available in the USA), mupirocin or bacitracin will suffice (Formulary 1, p. 334).

Ecthyma

This term describes ulcers forming under a crusted surface infection. The site may have been that of an insect bite or of neglected minor trauma. The bacterial
pathogens and their treatment are similar to those of impetigo; however, in contrast to impetigo, ecthyma heals with scarring.

**Furunculosis (boils)**

**Cause**

A boil is an acute pustular infection of a hair follicle, usually with *Staphylococcus aureus*. Adolescent boys are especially susceptible to them.

**Presentation and course**

A tender red nodule enlarges, and later may discharge pus and its central ‘core’ before healing to leave a scar. Fever and enlarged draining nodes complete the picture. Most patients have one or two boils only, and then clear; a few suffer from a tiresome sequence of boils (chronic furunculosis).

**Complications**

Cavernous sinus thrombosis is an unusual complication of boils on the central face. Septicaemia may occur but is rare.

**Differential diagnosis**

The diagnosis is straightforward but hidradenitis suppurativa (p. 161) should be considered if only the groin and axillae are involved.

**Investigations in chronic furunculosis**

- General examination: look for underlying skin disease (e.g. scabies, pediculosis, eczema).
- Test the urine for sugar. Full blood count.
- Culture swabs from lesions, and carrier sites (nostrils, perineum) of the patient and immediate family.
- Immunological evaluation only if the patient has recurrent or unusual internal infections too.

**Treatment**

Acute episodes will respond to an appropriate antibiotic; incision speeds healing.

In chronic furunculosis (Fig. 14.3):

- Treat carrier sites such as the nose and groin twice daily for 6 weeks with an appropriate topical antiseptic or antibiotic (e.g. chlorhexidine solution, mupirocin cream or clindamycin solution). Treat family carriers in the same way.

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**Fig. 14.3** Chronic furunculosis.
• Treat lesions with a topical antibiotic. In stubborn cases add 6 weeks of a systemic antibiotic chosen to cover organism’s proven sensitivities.
• Daily bath using an antiseptic soap.
• Improve hygiene and nutritional state, if faulty.

Carbuncle

A group of adjacent hair follicles becomes deeply infected with Staphylococcus aureus, leading to a swollen painful suppurating area discharging pus from several points. The pain and systemic upset are greater than those of a boil. Diabetes must be excluded. Treatment needs both topical and systemic antibiotics. Incision and drainage has been shown to speed up healing, although it is not always easy when there are multiple deep pus-filled pockets. Consider the possibility of a fungal kerion (p. 216) in unresponsive carbuncles.

Scalded skin syndrome

In this condition the skin changes resemble a scald. Erythema and tenderness are followed by the loosening of large areas of overlying epidermis (Fig. 14.4). In children the condition is usually caused by a staphylococcal infection elsewhere (e.g. impetigo or conjunctivitis). Organisms in what may be only a minor local infection release a toxin (exfoliatin) that causes a split to occur high in the epidermis. With systemic antibiotics the outlook is good.

This is in contrast to toxic epidermal necrolysis, which is usually drug-induced. The damage to the epidermis in toxic epidermal necrolysis is full thickness, and a skin biopsy will distinguish it from the scalded skin syndrome (p. 115).

Toxic shock syndrome

A staphylococcal toxin is also responsible for this condition, in which fever, a rash—usually a widespread erythema—and sometimes circulatory collapse are followed a week or two later by characteristic desquamation, most marked on the fingers and hands. Many cases have followed staphylococcal overgrowth in the vagina of women using tampons. Systemic antibiotics and irrigation of the infected site are needed.

Streptococcal infections

Erysipelas

The first warning of an attack is often malaise, shivering and a fever. After a few hours the affected area of skin becomes red, and the eruption spreads with a well-defined advancing edge. Blisters may develop on the red plaques (Fig. 14.5). Untreated, the condition can even be fatal, but it responds rapidly to systemic penicillin, sometimes given intravenously. The causative streptococci usually gain their entry through a split in the skin, e.g. between the toes or under an ear lobe.

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**LEARNING POINTS**

1. Look for head lice in the patient with recurrent impetigo of the head and neck.
2. The skin changes of the scalded skin syndrome, and of the toxic shock syndrome, are caused by staphylococcal exotoxins. Look for the primary infection elsewhere.
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which is a surgical emergency. At first the infection resembles a dusky, often painful, cellulitis, but it quickly turns into an extending necrosis of the skin and subcutaneous tissues. A deep ‘stab’ incision biopsy through the skin into the fascia may be necessary to obtain material for bacteriological culture. A magnetic resonance imaging (MRI) scan may help to establish how far the infection has spread. The prognosis is often poor despite early surgical debridement and prompt intravenous antibiotics, even when given before the bacteriological results are available.

Erysipeloid

It is convenient to mention this here, but the causative organism is *Erysipelothrix insidiosa* and not a streptococcus. It infects a wide range of animals, birds and fish. In humans, infections are most common in butchers, fishmongers and cooks, the organisms penetrating the skin after a prick from an infected bone. Such infections are usually mild, and localized to the area around the inoculation site. The swollen purple area spreads slowly with a clear-cut advancing edge. With penicillin the condition clears quickly; without it, resolution takes several weeks.

Cat-scratch disease

The infective agent is the bacillus *Rochalimaea henselae*. A few days after a cat bite or scratch, a reddish granulomatous papule appears at the site of inoculation. Tender regional lymphadenopathy follows some weeks later, and lasts for several weeks, often being accompanied by a mild fever. The glands may discharge before settling spontaneously. There is no specific treatment.

Spirochaetal infections

Syphilis

*Cause*

Infection with the causative organism, *Treponema pallidum*, may be congenital, acquired through transfusion with contaminated blood, or by accidental inoculation. The most important route, however, is through sexual contact with an infected partner.
are obvious lesions on the palms and soles. Annular lesions are also not uncommon. Condyloma lata are moist papules in the genital and anal areas. Other signs include a ‘moth-eaten’ alopecia and mucous patches in the mouth.

The skin lesions of late syphilis may be nodules that spread peripherally and clear centrally, leaving a serpiginous outline. Gummas are granulomatous areas; in the skin they quickly break down to leave punched-out ulcers that heal poorly, leaving papery white scars.

Clinical course

Even if left untreated, most of those who contract syphilis have no further problems after the secondary stage has passed. Others develop the cutaneous or systemic manifestations of late syphilis.

Differential diagnosis

The skin changes of syphilis can mimic many other skin diseases. Always consider the following.

1. Chancre: chancroid (multiple and painful), herpes simplex, anal fissure, cervical erosions.
2. Secondary syphilis:

Presentation

Congenital syphilis. If there is a high standard of antenatal care, syphilis in the mother will be detected and treated during pregnancy, and congenital syphilis will be rare. Otherwise, stillbirth is a common outcome, although some children with congenital syphilis may develop the stigmata of the disease only in late childhood.

Acquired syphilis. The features of the different stages are given in Fig. 14.6. After an incubation period (9–90 days), a primary chancre develops at the site of inoculation. Often this is genital, but oral and anal chancre are not uncommon. A typical chancre is an ulcerated, although not painful, button-like lesion of up to 1 cm in diameter accompanied by local lymphadenopathy. Untreated it lasts about 6 weeks and then clears leaving an inconspicuous scar.

The secondary stage may be reached while the chancre is still subsiding. Systemic symptoms and a generalized lymphadenopathy usher in eruptions that at first are macular and inconspicuous, and later papular and more obvious. Lesions are distributed symmetrically and are of a coppery ham colour. Sometimes they resemble pityriasis rosea. Classically, there

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**Fig. 14.6 The stages of syphilis.**
Yaws

Yaws is distributed widely across the poorer parts of the tropics. The spirochaete, *Treponema pallidum ssp. pertenue*, gains its entry through skin abrasions. After an incubation period of up to 6 months, the primary lesion, a crusting and ulcerated papule known as the ‘mother yaw’, develops at the site of inoculation; later it may enlarge to an exuberant raspberry-like swelling which lasts for several months before healing to leave an atrophic pale scar. In the secondary stage, other lesions may develop in any area but do so especially around the orifices. They are not unlike the primary lesion but are smaller and more numerous (‘daughter yaws’). Hyperkeratotic plaques may appear on the palms and soles. The tertiary stage is characterized by ulcerated gummatous skin lesions, hyperkeratosis of the palms and soles, and a painful periostitis that distorts the long bones. Serological tests for syphilis are positive. Treatment is with penicillin.

Lyme disease

The spirochaete *Borrelia burgdorferi* is responsible for this condition, named after the town in the USA where it was first recognized. It is transmitted to humans by ticks of the genus *Ixodes*, commonly harboured by deer. The site of the tick bite becomes the centre of a slowly expanding erythematous ring (‘erythema migrans’; Fig. 14.7). Later, many annular non-scaly plaques may develop. In the USA, a few of those affected develop arthritis and heart disease, both of which are less common in European cases. Other internal complications include meningitis and cranial nerve palsies. Treated early, the condition clears well with a 21-day course of oral amoxycillin or doxycycline: patients affected systemically need longer courses of parenteral antibiotics. Infection can be confirmed by serology, although this is usually negative in the first few weeks after inoculation.

Other infections

Cutaneous anthrax

This condition is usually acquired through contact with infected livestock or animal products such as wool.
absorbant assay (ELISA)—both of which are currently available only at reference laboratories. Before the results are available, it is wise to assume that the organism is penicillin- and tetracycline-resistant, and to start treatment with ciprofloxacin at 400 mg intravenously every 12 h or, for milder cases, ciprofloxacin 500 mg orally every 12 h. The latter dose is suitable for prophylactic use in those who are known to have been exposed to spores. A switch to an alternative regimen can be made once the antibiotic sensitivity of the organism has been established. At present, anthrax vaccine is in short supply; it requires six injections over 18 months, with subsequent boosters, to prevent anthrax.

Gonococcal septicaemia

Skin lesions are important clues to the diagnosis of this condition, in which the symptoms and signs of classical gonorrhoea are usually absent. The patient, usually a woman with recurring fever and joint pains, develops sparse crops of skin lesions, usually around the hands and feet. The grey, often haemorrhagic, vesicopustules are characteristic. Rather similar lesions are seen in chronic meningococcal septicaemia.

Mycobacterial infections

Tuberculosis

Most infections in the UK are caused by Mycobacterium tuberculosis. Mycobacterium bovis infection, endemic in cattle, can be spread to humans by milk, but human infection with this organism is now rare in countries where cattle have been vaccinated against tuberculosis and the milk is pasteurized. The steady decline of tuberculosis in developed countries has been reversed in some areas where AIDS is especially prevalent. Dormant tuberculosis of the skin can also be reactivated by systemic corticosteroids, immunosuppressants and new anti TNF biological agents.

Inoculation tuberculosis

Lupus vulgaris (Fig. 14.8) can follow the inoculation of tubercle bacilli into the skin of a person with high immunity, the direct spread of the organism from an underlying infected lymph node, or blood-borne spread from a pulmonary lesion. Lesions occur most often around the head and neck. A reddish-brown scaly
Investigations

Biopsy for:
- microscopy (tuberculoid granulomas);
- bacteriological culture; and
- detection of mycobacterial DNA by PCR.

Mantoux test.

Treatment

The treatment of all types of cutaneous tuberculosis should be with a full course of a standard multidrug antituberculosis regimen. There is no longer any excuse for the use of one drug alone.

Prevention

Outbreaks of pulmonary tuberculosis are reminders that this disease has not yet been conquered and that vigilance is important. Bacillus Calmette–Guérin (BCG) vaccination of schoolchildren, immunization of cattle and pasteurization of milk remain the most effective protective measures.

Leprosy

Cause

Mycobacterium leprae was discovered by Hansen in 1874, but has still not been cultured in vitro, although it can be made to grow in some animals (armadillos, mouse foot-pads, etc.). In humans the main route of infection is through nasal droplets from cases of lepromatous leprosy although, interestingly, some cases have occurred in Louisiana from eating infected armadillos.

Epidemiology

Some 15 million people suffer from leprosy. Most live in the tropics and subtropics, but the ease of modern travel means that some cases are seen in northern Europe and the USA.

Presentation

The range of clinical manifestations and complications depends upon the immune response of the patient (Fig. 14.9). Those with a high resistance develop a paucibacillary tuberculoid type (Fig. 14.10) and those
sified as ‘borderline’. Those most like the tuberculoid type are known as borderline tuberculoid (BT) and those nearest to the lepromatous type as borderline lepromatous (BL). The clinical differences between the two polar types are given in Fig. 14.12.

with low resistance a multibacillary lepromatous type. Nerve thickening is earlier and more marked in the tuberculoid than lepromatous type (Fig. 14.11). Between the extremes lies a spectrum of reactions clas-

**Fig. 14.9** The spectrum of leprosy: tuberculoid to lepromatous.

**Fig. 14.10** Tuberculoid leprosy: subtle depigmentation with a palpable erythematous rim at the upper edge.

**Fig. 14.11** The ‘leonine’ facies of lepromatous leprosy.
**Infections**

- Sarcoidosis, granuloma annulare, necrobiosis lipoidica.
- Lepromatous leprosy. Widespread leishmaniasis can closely simulate lepromatous leprosy. The nodules seen in neurofibromatosis and mycosis fungoides, and multiple sebaceous cysts, can cause confusion, as can the acral deformities seen in yaws and systemic sclerosis. Leprosy is a great imitator.

**Differential diagnosis**

**Tuberculoid leprosy.** Consider the following—in none of which is there any loss of sensation.
- Vitiligo (p. 246)—loss of pigment is usually complete.
- Pityriasis versicolor (p. 221)—scrapings show mycelia and spores.
- Pityriasis alba—a common cause of scaly hypopigmented areas on the cheeks of children.
- Postinflammatory depigmentation of any cause.

**Lepromatous leprosy.** Non-infectious.
Investigations

- Biopsy of skin or sensory nerve.
- Skin or nasal smears, with Ziehl–Nielsen or Fite stains, will show up the large number of organisms seen in the lepromatous type.
- Lepromin test. This is of no use in the diagnosis of leprosy but, once the diagnosis has been made, it will help to decide which type of disease is present (positive in tuberculoid type).

Treatment

The emergence of resistant strains of *M. leprae* means that it is no longer wise to treat leprosy with dapsone alone. It should now be used in combination, usually with rifampicin, and also with clofazimine for lepromatous leprosy. A brief period of isolation is needed only for patients with infectious lepromatous leprosy; with treatment they quickly become non-infectious and can return to the community. However, their management should remain in the hands of physicians with a special interest in the disease. Tuberculoid forms are usually treated for 6–12 months; multibacillary leprosy needs treatment for at least 2 years.

Special care is needed with the two types of lepra reaction that can occur during treatment:

- **Type 1 (reversal) reactions** are seen mainly in borderline tuberculoid disease (Fig. 14.13). Lesions become red and angry, and pain and paralysis follow neural inflammation. Treatment is with salicylates, chloroquine, non-steroidal and steroidal anti-inflammatory drugs.
- **Type 2 reactions** are common in lepromatous leprosy and include erythema nodosum, nerve palsies, lymphadenopathy, arthritis, iridocyclitis, epididymo-orchitis and proteinuria. They are treated with the drugs used for type 1 reactions, and also with thalidomide.

The household contacts of lepromatous patients are at risk of developing leprosy and should be followed up. Child contacts may benefit from prophylactic therapy and BCG inoculation.

Other mycobacterial infections

Mycobacteria are widespread in nature, living as environmental saprophytes. Some can infect humans.

*Mycobacterium marinum*

*M. marinum* lives in water. Human infections have occurred in epidemics centred on infected swimming pools. Another route of infection is through minor skin breaches in those who clean out tropical fish tanks (Fig. 14.14). After a 3-week incubation period, an indolent abscess or ulcerated nodule forms at the site of inoculation; later nodules may develop along the draining lymphatics (sporotrichoid spread; Fig. 14.15 and p. 222). The lesions heal spontaneously, but slowly. Resolution may be speeded by an 8-week course of trimethoprim/sulfamethoxazole or minocycline. Should these fail, rifampicin in combination with ethambutol is worth a trial.

*Mycobacterium ulcerans*

Infections are confined to certain humid tropical areas where the organism lives on the vegetation, and are most common in Uganda (Buruli ulcers). The necrotic spreading ulcers, with their undermined edges, are usually found on the legs. Drug therapy is often disappointing and the treatment of choice is probably the surgical removal of infected tissue.
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• culture; and
• polymerase chain reaction tests.

Treatment

Single nodules often resolve spontaneously and may not need treatment. Destructive measures, including cryotherapy, are sometimes used for localized skin lesions. Oral zinc sulphate (5 mg/kg/day for 4 weeks) showed promising results in a recent Indian trial.

Intralesional or intravenous antimony compounds are still the treatment of choice for most types of leishmaniasis, e.g. sodium stibogluconate (20 mg/kg/day for 20 days) with regular blood tests and electrocardiographic monitoring.

Viral infections

The viral infections dealt with here are those that are commonly seen in dermatology clinics. A textbook of infectious diseases should be consulted for details of systemic viral infections, many of which, like measles and German measles, have their own specific rashes.

Viral warts

Most people will have a wart at some time in their lives. Their prevalence is highest in childhood, and they affect an estimated 4–5% of schoolchildren in the UK.

Cause

Warts are caused by the human papilloma virus (HPV), which has still not been cultured in vitro. Nevertheless,
more than 70 ‘types’ of the virus have been recognized by DNA sequencing; each has its own range of clinical manifestations. HPV-1, 2 and 4, for example, are found in common warts, whereas HPV-3 is found in plane warts, and HPV-6, 11, 16 and 18 are most common in genital warts. Infections occur when wart virus in skin scales comes into contact with breaches in the skin or mucous membranes.

**Presentation**

Warts adopt a variety of patterns (Fig. 14.17), some of which are described below.

*Common warts* (Figs 14.18 and 14.19). The first sign is a smooth skin-coloured papule, often more easily felt than seen. As the lesion enlarges, its irregular hyperkeratotic surface gives it the classic ‘warty’ appearance. Common warts usually occur on the hands but are also often on the face and genitals. They are more often multiple than single. Pain is rare.

*Plantar warts*. These have a rough surface, which protrudes only slightly from the skin and is surrounded by a horny collar (Fig. 14.20). On paring, the presence of bleeding capillary loops allows plantar warts to be distinguished from corns. Often multiple, plantar warts can be painful.
an immunological reaction, just before they resolve spontaneously. Lesions are multiple, painless and, like common warts, are sometimes arranged along a scratch line.

**Facial warts.** These are most common in the beard area of adult males and are spread by shaving. A digitate appearance is common. Lesions are often ugly but are painless.

**Anogenital warts** (*condyloma acuminata*) (Fig. 14.23). Papillomatous cauliflower-like lesions, with a moist macerated vascular surface, can appear anywhere in this area. They may coalesce to form huge lesions causing discomfort and irritation. The vaginal and anorectal mucosae may be affected. The presence of anogenital warts in children raises the spectre of sexual abuse, but is usually caused by autoinoculation from common warts elsewhere.

**Course**

Warts resolve spontaneously in the healthy as the immune response overcomes the infection. This happens within 6 months in some 30% of patients, and within 2 years in 65%. Such spontaneous resolution, sometimes heralded by a punctate blackening caused by capillary thrombosis (Fig. 14.24), leaves no trace. Mosaic warts are notoriously slow to resolve and often resist all treatments. Warts persist and spread in immunocompromised patients (e.g. those on immunosuppressive therapy or with lymphoreticular disease).
defined. If in doubt, look for other signs of secondary syphilis (p. 193) and carry out serological tests.
• Amelanotic melanomas and other epithelial malignancies can present as verrucose nodules—those in patients over the age of 40 years should be examined with special care. Mistakes have been made in the past.

Treatment

Many warts give no trouble, need no treatment and will go away by themselves. Otherwise treatment will depend on the type of wart. In general terms, destruction by cryotherapy is less likely to cause scars than excision or electrosurgery.

Palmoplantar warts

Home treatment is best, with one of the many wart paints now available (Formulary 1, p. 335). Most contain salicylic acid (12–20%). The success rate is good if the patient is prepared to persist with regular treatment. Paints should be applied once daily, after moistening the warts in hot water for at least 5 min. After drying, dead tissue and old paint are removed with an emery board or pumice stone. Enough paint to cover the surface of the wart, but not the surrounding skin, is applied and allowed to dry. Warts on the plantar surface should be covered with plasters although this is not necessary elsewhere. Side-effects are rare if these instructions are followed. Wart paints should not be applied to facial or anogenital skin, or to patients with adjacent eczema.

If no progress is being made after the regular and correct use of a salicylic acid wart paint for 12 weeks, then a paint containing formaldehyde or glutaraldehyde is worth trying. A useful way of dealing with multiple small plantar warts is for the area to be soaked for 10 min each night in a 4% formalin solution, although a few patients become allergic to this.

Cryotherapy with liquid nitrogen (at –196°C) is more effective than the less cold, dry ice or dimethyl ether/propane techniques. However, it is painful. A cotton-tipped applicator dipped into liquid nitrogen is applied to the wart until a small frozen halo appears in the surrounding normal skin (Fig. 14.25). The human papilloma virus, and also other viruses such as HIV, can survive in stored liquid nitrogen and so, once used, a bud should not be dipped back into the flask. Treatment with a liquid nitrogen spray gun does not

Seventy per cent of renal allograft recipients will have warts 5 years after transplantation.

Complications

1 Some plantar warts are very painful.
2 Epidermodysplasia verruciformis is a rare inherited disorder in which there is a universal wart infection, usually with HPV of unusual types. An impairment of cell-mediated immunity (p. 26) is commonly found and ensuing carcinomatous change frequently occurs.
3 Malignant change is otherwise rare, although infections with HPV of certain genital strains predispose to cervical and penile carcinoma. HPV infections in immunocompromised patients (e.g. renal allograft recipients) have also been linked with skin cancer, especially on light-exposed areas.

Differential diagnosis

Most warts are easily recognized. The following must be ruled out.
• Molluscum contagiosum (p. 209) are smooth, dome-shaped and pearly, with central umbilication.
• Plantar corns are found on pressure areas; there is no capillary bleeding on paring. They have a central keratotic core and are painful.
• Granuloma annulare lesions (p. 284) have a smooth surface, as the lesions are dermal; and their outline is often annular.
• Condyloma lata are seen in syphilis. They are rare but should not be confused with condyloma acuminata (warts). The lesions are flatter, greyer and less well

Fig. 14.24 Spontaneous resolution of a group of plantar warts. The blackness is caused by capillary thrombosis.
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before powdering with talcum. On the first occasion it should be washed off with soap and water after 2 h but, if there has been little discomfort, this can be increased stepwise to 6 h. Treatment is best carried out weekly by a doctor or nurse, but not by the patient. Podophyllin must not be used in pregnancy. Cryotherapy, electrosurgery and laser treatment are all effective treatments in the clinic.

Facial common warts

These are best treated with electrocautery or a hyfrecator, but also surrender to careful cryotherapy. Scarring is an unwanted complication. Shaving, if essential, should be with a brushless foam and a disposable razor.

Plane warts

On the face these are best left untreated and the patient or parent can be reasonably assured that spontaneous resolution will occur. When treatment is demanded, the use of a wart paint or imiquimod cream is reasonable. Gentle cryotherapy of just a few warts may help to induce immunity.

Solitary, stubborn or painful warts

These can be removed under local anaesthetic with a curette, although cure is not assured with this or any other method, and a scar often follows. Surgical excision is never justifiable (Fig. 14.26). Bleomycin can also be injected into such warts with success but this treatment should only be undertaken by a specialist.

Anogenital warts

Women with anogenital warts, or who are the partners of men with anogenital warts, should have their cervical cytology checked regularly as the wart virus can cause cervical cancer.

The focus has shifted towards self-treatment using podophyllotoxin (0.5% solution or 0.15% cream) or imiquimod (5% cream). Both are irritants and should be used carefully according to the manufacturer’s instructions. Imiquimod is an immune response modifier that induces keratinocytes to produce cytokines, leading to wart regression, and may help to build cell-mediated immunity for longlasting protection. It is applied as a thin layer three times weekly and washed off with a mild soap 6–10 h after application. Podophyllin paint (15%) is used much less often now. It should be applied carefully to the warts and allowed to dry

Fig. 14.25 A wart treated with cryotherapy: area includes a small frozen halo of normal surrounding skin.

Fig. 14.26 Multiple scars following the injudicious surgical treatment of warts.
Investigations
None are usually needed.

Treatment
Aciclovir, famciclovir and valaciclovir (Formulary 2, p. 344) should be reserved for severe attacks and for immunocompromised patients; for the latter, prophylactic aciclovir can also be used to prevent disease if given within a day or two of exposure. In mild attacks, calamine lotion topically is all that is required. A live attenuated vaccine is now available, and being more widely used. It is not universally effective and should not be given to patients with immunodeficiencies or blood dyscrasias who might not be able to resist even the attenuated organism.

Herpes zoster

Cause
Shingles too is caused by the herpes virus varicella-zoster. An attack is a result of the reactivation, usually for no obvious reason, of virus that has remained dormant in a sensory root ganglion since an earlier episode of chickenpox (varicella). The incidence of shingles is highest in old age, and in conditions such as Hodgkin’s disease, AIDS and leukaemia, which weaken normal defence mechanisms. Shingles does not occur in epidemics; its clinical manifestations are caused by virus acquired in the past. However, patients with zoster can transmit the virus to others in whom it will cause chickenpox (Fig. 14.27).

Presentation and course
Attacks usually start with a burning pain, soon followed by erythema and grouped, sometimes blood-filled, vesicles scattered over a dermatome. The clear vesicles quickly become purulent, and over the space of a few days burst and crust. Scabs usually separate in 2–3 weeks, sometimes leaving depressed depigmented scars.

Zoster is characteristically unilateral (Fig. 14.28). It may affect more than one adjacent dermatome. The thoracic segments and the ophthalmic division of the trigeminal nerve are involved disproportionately often.

Varicella (chickenpox)

Cause
The herpes virus varicella-zoster is spread by the respiratory route; its incubation period is about 14 days.

Presentation and course
Slight malaise is followed by the development of papules, which turn rapidly into clear vesicles, the contents of which soon become pustular. Over the next few days the lesions crust and then clear, sometimes leaving white depressed scars. Lesions appear in crops, are often itchy, and are most profuse on the trunk and least profuse on the periphery of the limbs (centripetal). Second attacks are rare. Varicella can be fatal in those who are immunologically compromised.

Complications
• Pneumonitis, with pulmonary opacities on X-ray.
• Secondary infection of skin lesions.
• Haemorrhagic or lethal chickenpox in the immunocompromised.
• Scarring.

Differential diagnosis
Smallpox, mainly centrifugal anyway, has been universally eradicated, and the diagnosis of chickenpox is seldom in doubt.
particularly if the lesions are unusually haemorrhagic or necrotic.

**Complications**

- Secondary bacterial infection is common.
- Motor nerve involvement is uncommon, but has led to paralysis of ocular muscles, the facial muscles, the diaphragm and the bladder.
- Zoster of the ophthalmic division of the trigeminal nerve can lead to corneal ulcers and scarring. A good clinical clue here is involvement of the nasociliary branch (vesicles grouped on the side of the nose).
- Persistent neuralgic pain, after the acute episode is over, is most common in the elderly.

**Differential diagnosis**

Occasionally, before the rash has appeared, the initial pain is taken for an emergency such as acute appendicitis or myocardial infarction. Otherwise,
the dermatomal distribution, and the pain, allow zoster to be distinguished easily from herpes simplex, eczema and impetigo.

Investigations

Cultures are of little help as they take 5–7 days, and are only positive in 70% of cases. Biopsy or Tzanck smears show multinucleated giant cells and a ballooning degeneration of keratinocytes, indicative of a herpes infection. Any clinical suspicions about underlying conditions, such as Hodgkin’s disease, chronic lymphatic leukaemia or AIDS, require further investigation.

Treatment

Systemic treatment should be given to all patients if diagnosed in the early stages of the disease. It is essential that this treatment should start within the first 5 days of an attack. Famiclovir and valaciclovir are as effective as aciclovir (Formulary 2, p. 344); they depend on virus-specific thymidine kinase for their antiviral activity. All three drugs are safe, and using them may cut down the chance of getting postherpetic neuralgia, particularly in the elderly.

If diagnosed late in the course of the disease, systemic treatment is not likely to be effective and treatment should be supportive with rest, analgesics and bland applications such as calamine. Secondary bacterial infection should be treated appropriately.

A trial of systemic carbamazepine, gabapentin or amitriptyline, or 4 weeks of topical capsaicin cream (Formulary 1, p. 339), despite the burning sensation it sometimes causes, may be worthwhile for established post-herpetic neuralgia.

**Learning Points**

1. Post-herpetic neuralgia affects the elderly rather than the young.
2. Systemic aciclovir works best if given early in the course of the disease.
3. Look for an underlying cause when there is dissemination outside the main affected dermatomes.

**Herpes simplex**

**Cause**

Herpesvirus hominis is the cause of herpes simplex. The virus is ubiquitous and carriers continue to shed virus particles in their saliva or tears. It has been separated into two types. The lesions caused by type II virus occur mainly on the genitals, while those of type I are usually extragenital; however, this distinction is not absolute.

The route of infection is through mucous membranes or abraded skin. After the episode associated with the primary infection, the virus may become latent, possibly within nerve ganglia, but still capable of giving rise to recurrent bouts of vesication (recrudescences).

**Presentation**

**Primary infection**

The most common recognizable manifestation of a primary type I infection in children is an acute gingivostomatitis accompanied by malaise, headache, fever and enlarged cervical nodes. Vesicles, soon turning into ulcers, can be seen scattered over the lips and mucous membranes. The illness lasts about 2 weeks.

Primary type II virus infections, usually transmitted sexually, cause multiple and painful genital or perianal blisters which rapidly ulcerate.

The virus can also be inoculated directly into the skin (e.g. during wrestling). A herpetic whitlow is one example of this direct inoculation. The uncomfortable pus-filled blisters on a fingertip are seen most often in medical personnel attending patients with unsuspected herpes simplex infections.

**Recurrent (recrudescent) infections**

These strike in roughly the same place each time. They may be precipitated by respiratory tract infections (cold sores), ultraviolet radiation, menstruation or even stress. Common sites include the face (Fig. 14.29) and lips (type I), and the genitals (type II), but lesions can occur anywhere. Tingling, burning or even pain is followed within a few hours by the development of erythema and clusters of tense vesicles. Crusting occurs within 24–48 h and the whole episode lasts about 12 days.
of the episode, cuts down the length of attacks and perhaps increases the intervals between them.

Aciclovir tablets (Formulary 2, p. 344), 200 mg five times daily for 5 days, is more effective and can be given to those with widespread or systemic involvement. Recurrences in the immunocompromised can usually be prevented by long-term treatment at a lower dosage. Famciclovir and valaciclovir are metabolized by the body into aciclovir and are as effective as aciclovir, having the additional advantage of needing fewer doses per day.

**Molluscum contagiosum**

**Cause**

This common pox virus infection can be spread by direct contact; e.g. sexually or by sharing a towel at the swimming bath.

**Presentation and course**

The incubation period ranges from 2 to 6 weeks. Often several members of one family are affected. Individual lesions are shiny, white or pink, and hemispherical; they grow slowly up to 0.5 cm in diameter. A central punctum, which may contain a cheesy core, gives the lesions their characteristic umbilicated look. On close inspection a mosaic appearance may be seen. Multiple lesions are common (Fig. 14.30) and their distribution depends on the mode of infection. Atopic individuals and the immunocompromised are prone to especially extensive infections, spread by scratching and the use of topical steroids.

**Complications**

- Herpes encephalitis or meningitis can occur without any cutaneous clues.
- Disseminated herpes simplex: widespread vesicles may be part of a severe illness in newborns, debilitated children or immunosuppressed adults.
- Eczema herpeticum: patients with atopic eczema are particularly susceptible to widespread cutaneous herpes simplex infections. Those looking after patients with atopic eczema should stay away if they have cold sores.
- Herpes simplex can cause recurrent dendritic ulcers leading to corneal scarring.
- In some patients, recurrent herpes simplex infections are regularly followed by erythema multiforme (p. 99).

**Investigations**

None are usually needed. Doubts over the diagnosis can be dispelled by culturing the virus from vesicle fluid. Antibody titres rise with primary, but not with recurrent infections.

**Treatment**

‘Old-fashioned’ remedies suffice for occasional mild recurrent attacks; sun block may cut down their frequency. Dabbing with surgical spirit is helpful, and secondary bacterial infection can be reduced by topical bacitracin, mupirocin, framycetin or fusidic acid. For more severe and frequent attacks, aciclovir cream, if used at the first sign of the recrudescence, and applied five or six times a day for the first 4 days of the episode, cuts down the length of attacks and perhaps increases the intervals between them.

Aciclovir tablets (Formulary 2, p. 344), 200 mg five times daily for 5 days, is more effective and can be given to those with widespread or systemic involvement. Recurrences in the immunocompromised can usually be prevented by long-term treatment at a lower dosage. Famciclovir and valaciclovir are metabolized by the body into aciclovir and are as effective as aciclovir, having the additional advantage of needing fewer doses per day.
Sometimes a local anaesthetic cream (EMLA; see Formulary 1, p. 339), under polythene occlusion for an hour, will help children to tolerate more attacking treatment. Sparse eyelid lesions can be left alone but patients with numerous lesions may need to be referred to an ophthalmologist for curettage. Common sense measures help to limit spread within the family.

**Orf**

**Cause**

Contagious pustular dermatitis is common in lambs. Its cause is a parapox virus that can be transmitted to those handling infected animals. The condition is therefore most commonly seen on the hands of shepherds, of their wives who bottle-feed lambs, and of butchers, vets and meat porters.

**Presentation and course**

The incubation period is 5–6 days. Lesions, which may be single or multiple, start as small firm papules that change into flat-topped apparently pustular nodules with a violaceous and erythematous surround (Fig. 14.31). The condition clears up spontaneously in about a month.

**Complications**

- Lymphadenitis and malaise are common.
- Erythema multiforme.
- ‘Giant’ lesions can appear in the immunosuppressed.

**Differential diagnosis**

Infamed lesions can simulate a boil. Large solitary lesions in adults can be confused with a keratocanthoma (p. 262), an intradermal naevus (p. 259), or even a cystic basal cell carcinoma (p. 266). Confusion with warts should not arise as these have a rough surface and no central pore.

**Investigations**

None are usually needed, but the diagnosis can be confirmed by looking under the microscope for large swollen epidermal cells, easily seen in unstained preparations of debris expressed from a lesion.

**Treatment**

Many simple destructive measures cause inflammation and then resolution. They include squeezing out the lesions with forceps, piercing them with an orange stick (preferably without phenol), and curettage. Liquid nitrogen may also be helpful.

These measures are fine for adults, but young children dislike them and it is reasonable to play for time using imiquimod or chlortetracycline cream, or instructing the mother carefully how to apply a wart paint once a week to lesions well away from the eyes.

**Learning Points**

1. If you cannot tell mollusca from warts, buy a lens.
2. Do not hurt young children with mollusca. You will not be able to get near them next time something more serious goes wrong.
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Diff erential diagnosis

Diagnosis is usually simple if contact with sheep is recognized. Milker’s nodules, a pox virus infection acquired from cow’s udders, can look like orf, as can staphylococcal furuncles.

Investigations

None are usually needed. If there is any doubt, the diagnosis can be confirmed by the distinctive electron microscopic appearance of the virus obtained from crusts.

Treatment

A topical antibiotic helps to prevent secondary infection; otherwise no active therapy is needed.

Acquired immunodeficiency syndrome (AIDS)

The AIDS epidemic was first recognized in the USA in 1981. The early cases were male homosexuals with pneumocystis pneumonia or Kaposi’s sarcoma and immunosuppression. Later it became clear that the human immunodeficiency virus (HIV) could be acquired from contaminated body fluids, particularly semen and blood, in many ways, the importance of which varies from country to country. In the UK and the USA, for example, most cases have been homosexual or bisexual men; in parts of Africa, on the other hand, the disease is most often spread heterosexually.

Other groups at high risk are intravenous drug abusers who share contaminated needles and syringes, and haemophiliacs who were given infected blood products. Up to a half of babies born to infected mothers will be infected transplacentally.

The global epidemic is not slackening off though the pattern of transmission in industrialized nations is changing. Heterosexual transmission now accounts for 25–30% of new cases in Europe and the USA. In 1999, about 5.4 million people were newly infected with HIV.

Pathogenesis

The human immunodeficiency viruses, HIV-1 and HIV-2 (mainly in West Africa), are RNA retroviruses containing reverse transcriptase enzymes, which allow the viral DNA copy to be incorporated into the chromosomes of the host cell. Their main target is a subset of T lymphocytes (helper/inducer cells) that express glycoprotein CD4 molecules on their surface (p. 19). These bind to the surface envelope of the HIV. Viral replication within the helper/inducer cells kills them, and their depletion leads to the loss of cell-mediated immunity so characteristic of HIV infection. A variety of opportunistic infections may then follow.

Course

The original infection may be asymptomatic, or followed by a glandular fever-like illness at the time of seroconversion. After a variable latent phase, which may last several years, a persistent generalized lymphadenopathy develops. The term ‘AIDS-related complex’ refers to the next stage, in which many of the symptoms of AIDS (e.g. fever, weight-loss, fatigue or diarrhoea) may be present without the opportunistic infections or tumours characteristic of full-blown AIDS. Not all of those infected with HIV will develop AIDS but, for those who do, the average time from infection to the onset of AIDS is about 10 years. Once AIDS develops, if untreated, about half will die within 1 year and three-quarters within 4 years.

Skin changes in AIDS

Skin conditions are often the first clue to the presence of AIDS. The following are important:

1 Kaposi’s sarcoma (Figs 14.32–14.34) is the initial presentation in a decreasing percentage of AIDS patients, particularly homosexual men. The lesions of classical Kaposi’s sarcoma are multiple purplish patches or nodules (see Fig. 19.49). In AIDS the lesions may be atypical, sometimes looking like bruises or pyogenic granulomata (p. 277). The diagnosis can easily be missed and the mouth must always be examined.

2 Seborrhoeic eczema and folliculitis (Fig. 14.35) are seen in at least 50% of patients, often starting at an early stage of immunosuppression. The underlying cause may be an overgrowth of Pityrosporum yeasts. An itchy folliculitis of the head, neck and trunk, and an eosinophilic folliculitis, possibly as a result of the multiplication of Demodex folliculorum, have also been described.

3 Skin infections—florid, unusually extensive or atypical examples of common infections may be seen with
Other manifestations

Dry skin is common in AIDS; so is pruritus. Psoriasis may start or worsen with AIDS. Diffuse alopecia is not uncommon. Drug eruptions are often seen in AIDS patients.

Management

The clinical diagnosis of HIV infection is confirmed by a positive blood test for antibodies to the virus. Patients should be counselled before and after testing. 

4 Other manifestations—dry skin is common in AIDS; so is pruritus. Psoriasis may start or worsen with AIDS. Diffuse alopecia is not uncommon. Drug eruptions are often seen in AIDS patients.
for HIV antibody. Sexual contacts of infected individuals should be traced.

Modern drugs for HIV infections increase life expectancy, but are not ‘cures’ in the usual sense. They reduce the viral load but are expensive and sometimes toxic. Guidelines on how to use them change constantly, and so the drug treatment of HIV infections should be directed by specialists in the field, who will monitor the plasma viral load and CD4 count regularly (Table 14.1). Difficult decisions to be made include the timing of treatment—the benefits of starting early have to be balanced against the risk of toxicity—and choosing the right drug combination of highly active antiretroviral treatment (HAART)—usually triple therapy with two nucleoside reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. The regimen will be changed if there is clinical or virological deterioration, or if the patient becomes pregnant, although the teratogenic potential of most of these drugs is still not known.

Treatment otherwise is symptomatic and varies according to the type of opportunistic infection detected. Prophylactic treatment against a number of life-threatening infections is also worthwhile, and prolongs life expectancy. Educating the public to avoid risky behaviour, such as unprotected sexual intercourse, is still hugely important.

Mucocutaneous lymph node syndrome (Kawasaki’s disease)
The cause may be a recent parvovirus infection. The disease affects young children whose erythema, although often generalized, becomes most marked in a glove and stocking distribution; it may be associated with indurated oedema of the palms and soles. Peeling around the fingers and toes is one obvious feature but is not seen at the start. Bilateral conjunctival injection and erythema of the lips, buccal mucosa and tongue (‘strawberry tongue’) are common.

The episode is accompanied by fever and usually resolves within 2 weeks. Despite its name, not all patients have lymphadenopathy. The danger of this condition lies in the risk of developing myocarditis and coronary artery disease. The pathology is close to that of polyarteritis nodosa. Aspirin and intravenous gammaglobulin are the mainstay of treatment; both should be given early in the disease and reduce the risk of coronary artery involvement.

Gianotti–Crosti syndrome
This is a rather uncommon reaction to an infection with hepatitis B virus in childhood. Small reddish papules erupt bilaterally over the limbs and face, and fade over the course of a few weeks. Jaundice is uncommon, although tests of liver function give abnormal results.

Herpangina
This is an acute infectious illness, caused by group A Coxsackie viruses. The patient is usually a child with a fever, and a severe sore throat covered in many small vesicles, which rapidly become superficial ulcers. Episodes resolve in about a week.

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Decision</th>
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<tbody>
<tr>
<td>Symptomatic</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt; 200 × 10^6/L</td>
<td>Treat</td>
</tr>
<tr>
<td>CD4 200–350 × 10^6/L</td>
<td>Treatment generally offered</td>
</tr>
<tr>
<td>CD4 &gt; 350 × 10^6/L</td>
<td>Defer treatment unless high viral load</td>
</tr>
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</table>
pink macular rash, which fades, first on the trunk, over the course of a few days. Rubella during the first trimester of pregnancy carries a risk of damage to the unborn child. Prevention is by immunization with the combined MMR vaccine.

**Erythema infectiosum (fifth disease)**

This is caused by the human parvovirus B19 and occurs in outbreaks, often in the spring. A slapped cheek erythema is quickly followed by a reticulate erythema of the shoulders. The affected child feels well, and the rash clears over the course of a few days. Other features, sometimes not accompanied by a rash, include transient anaemia and arthritis.

**Fungal infections**

**Dermatophyte infections (ringworm)**

**Cause**

Three genera of dermatophyte fungi cause tinea infections (ringworm).
- *Trichophyton*—skin, hair and nail infections.
- *Microsporum*—skin and hair.
- *Epidermophyton*—skin and nails.

Dermatophytes invade keratin only, and the inflammation they cause is due to metabolic products of the fungus or to delayed hypersensitivity. In general, zoophilic fungi (those transmitted to humans by animals) cause a more severe inflammation than anthropophilic ones (spread from person to person).

**Presentation and course**

This depends upon the site and on the strain of fungus involved.

**Tinea pedis (athlete's foot)**

This is the most common type of fungal infection in humans. The sharing of wash places (e.g. in showers) and of swimming pools, predisposes to infection; occlusive footwear encourages relapses.

Most cases are caused by one of three organisms: *Trichophyton rubrum* (the most common and the
Tinea of the nails

Toenail infection is usually associated with tinea pedis. The initial changes occur at the free edge of the nail, which becomes yellow and crumbly (Fig. 14.40). Subungual hyperkeratosis, separation of the nail from its bed, and thickening may then follow. Usually only a few nails are infected but rarely all are. Fingernail lesions are similar, but less common, and are seldom seen without a chronic *T. rubrum* infection of the skin of the hands.

Tinea of the hands

This is usually asymmetrical and associated with tinea pedis. *T. rubrum* may cause a barely perceptible erythema of one palm with a characteristic powdery scale in the creases.

Tinea of the groin

This is common and affects men more often than women. The eruption is sometimes unilateral or asymmetrical. The upper inner thigh is involved and lesions expand slowly to form sharply demarcated plaques with peripheral scaling (Fig. 14.41). In contrast to candidiasis of the groin area, the scrotum is usually spared. A few vesicles or pustules may be seen within the lesions. The organisms are the same as those causing tinea pedis.
inflammation and hairs broken off 3–4 mm from the scalp. In favus, caused by Trichophyton schoenleini, the picture is dominated by foul-smelling yellowish crusts surrounding many scalp hairs, and sometimes leading to scarring alopecia.

Complications

1 Fierce animal ringworm of the scalp (Fig. 14.43) can lead to a permanent scarring alopecia.
scraping should be taken from the scaly margin of a lesion, with a small curette or a scalpel blade, and clippings/scrapings from the most crumbly part of a nail. Broken hairs should be plucked with tweezers. Specimens are cleared in potassium hydroxide (p. 35). Branching hyphae can easily be seen (see Fig. 3.7) using a scanning (×10) or low-power (×25) objective lens, with the iris diaphragm almost closed, and the condenser racked down. Hyphae may also be seen within a cleared hair shaft, or spores may be noted around it.

Cultures should be carried out in a mycology or bacteriology laboratory. Transport medium is not necessary, and specimens should be sent in folded black paper. The report may take as long as a month; microscopy is much quicker.

Wood’s light (ultraviolet light) examination of the scalp usually reveals a green fluorescence of the hairs in Microsporum audouini and M. canis infections. The technique is useful for screening children in institutions where outbreaks of tinea capitis still sometimes occur, but some fungi (e.g. Trichophyton tonsurans) do not fluoresce.

Treatment

Local

This is all that is needed for minor skin infections. The more recent imidazole preparations (e.g. miconazole and clotrimazole) and the allylamines such as terbinafine (Formulary 1, p. 335), have largely superseded time-honoured remedies such as benzoic acid ointment (Whitfield’s ointment) and tolnaftate. They should be applied twice daily. Magenta paint (Castellani’s paint), although highly coloured, is helpful for exudative or macerated areas in body folds or toe webs. Occasional dusting with an antifungal powder is useful to prevent relapses.

Topical nail preparations. Many patients now prefer to avoid systemic treatment. For them a nail lacquer containing amorolfine is worth a trial. It should be applied once or twice a week for 6 months; it is effective against stubborn moulds such as Hendersonula and Scopulariopsis. Both amorolfine and tioconazole nail solutions (Formulary 1, p. 335) can be used as adjuncts to systemic therapy (see below).
CHAPTER 14

Itraconazole (Formulary 2, p. 343) is now preferred to ketoconazole, which occasionally damages the liver, and is a reasonable alternative to terbinafine and griseofulvin if these are contraindicated. It is effective in tinea corporis, cruris and pedis; and also in nail infections, although without a licence for this use in many countries. Fungistatic rather than fungicidal, it interferes with the cytochrome P-450 system, so a review of any other medication being taken is needed before a prescription is issued. Its wide spectrum makes it useful also in pityriasis versicolor and candidiasis.

Candidiasis

Cause

Candida albicans is a classic opportunistic pathogen. Even in transient and trivial local infections in the apparently fit, one or more predisposing factors such as obesity, moisture and maceration, diabetes, pregnancy, the use of broad-spectrum antibiotics, or perhaps the use of the contraceptive pill, will often be found to be playing some part. Opportunism is even more obvious in the overwhelming systemic infections of the immunocompromised (Fig. 14.45).

Presentation

This varies with the site (Fig. 14.46).

Oral candidiasis (see also Chapter 13)

One or more whitish adherent plaques (like bread sauce) appear on the mucous membranes. If wiped off they leave an erythematous base. Under dentures, candidiasis will produce sore red areas. Angular stomatitis, usually in denture wearers (Fig. 14.47), may be candidial.

LEARNING POINTS

1. Do not prescribe griseofulvin, terbinafine or itraconazole for psoriasis of the nails or chronic paronychia. Get mycological proof first.
2. Your patient’s asymmetrical ‘eczema’ is spreading despite local steroids—think of a dermatophyte infection.
3. Consider tinea in acute inflammatory and purulent reactions of the scalp and beard.
INFECTIONS

amounts of pus can be expressed. The adjacent nail plate becomes ridged and discoloured. Predisposing factors include wet work, poor peripheral circulation and vulval candidiasis.

Chronic mucocutaneous candidiasis

Persistent candidiasis, affecting most or all of the areas described above, can start in infancy. Sometimes the nail plates as well as the nail folds are involved. Candida granulomas may appear on the scalp. Several different forms have been described including those with autosomal recessive and domin­ant inheritance patterns. In the Candida endocrinopathy syndrome, chronic candidiasis occurs with one or more endocrine defects, the most common of which are hypoparathyroidism, and Addison’s disease. A few late-onset cases have underlying thymic tumours.

Genital candidiasis

Most commonly presents as a sore itchy vulvovaginitis, with white curdy plaques adherent to the inflamed mucous membranes, and a whitish discharge. The eruption may extend to the groin folds. Conjugal spread is common; in males similar changes occur under the foreskin (Fig. 14.48) and in the groin.

Diabetes, pregnancy and antibiotic therapy are common predisposing factors.

Paronychia

Acute paronychia is usually bacterial, but in chronic paronychia Candida may be the sole pathogen, or be found with other opportunists such as Proteus or Pseudomonas. The proximal and sometimes the lateral nail folds of one or more fingers become bolstered and red (see Fig. 13.28). The cuticles are lost and small amounts of pus can be expressed. The adjacent nail plate becomes ridged and discoloured. Predisposing factors include wet work, poor peripheral circulation and vulval candidiasis.

Chronic mucocutaneous candidiasis

Persistent candidiasis, affecting most or all of the areas described above, can start in infancy. Sometimes the nail plates as well as the nail folds are involved. Candida granulomas may appear on the scalp. Several different forms have been described including those with autosomal recessive and dominant inheritance patterns. In the Candida endocrinopathy syndrome, chronic candidiasis occurs with one or more endocrine defects, the most common of which are hypoparathyroidism, and Addison’s disease. A few late-onset cases have underlying thymic tumours.

Fig. 14.45  Factors predisposing to the different types of candidiasis.
immunological work-up will be needed, focusing on cell-mediated immunity.

Treatment

Predisposing factors should be sought and eliminated; e.g. denture hygiene may be important. Infected skin folds should be separated and kept dry. Those with chronic paronychia should keep their hands warm and dry.
Amphotericin, nystatin and the imidazole group of compounds are all effective topically. For the mouth, these are available as oral suspensions, lozenges and oral gels (Formulary 1, p. 334). False teeth should be removed at night, washed and steeped in a nystatin solution. For other areas of candidiasis, creams, ointment and pessaries are available (Formulary 1, p. 335). Magenta paint is also a useful but messy remedy for the skin flexures. In chronic paronychia, the nail folds can be packed with an imidazole cream or drenched in an imidazole solution several times a day. Genital candidiasis responds well to a single day’s treatment with either itraconazole and fluconazole (Formulary 2, p. 343). Both are also valuable for recurrent oral candidiasis of the immunocompromised, and for the various types of chronic mucocutaneous candidiasis.

Pityriasis versicolor

Cause

The old name, tinea versicolor, should be dropped as the disorder is caused by commensal yeasts (*Pityrosporum orbiculare*) and not by dermatophyte fungi. Overgrowth of these yeasts, particularly in hot humid conditions, is responsible for the clinical lesions.

Carboxylic acids released by the organisms inhibit the increase in pigment production by melanocytes that occurs normally after exposure to sunlight. The term ‘versicolor’ refers to the way in which the superficial scaly patches, fawn or pink on non-tanned skin (Fig. 14.49), become paler than the surrounding skin after exposure to sunlight (Fig. 14.50). The condition should be regarded as non-infectious.

Presentation and course

The fawn or depigmented areas, with their slightly branny scaling and fine wrinkling, look ugly. Other-

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**LEARNING POINTS**

1. Always check the urine for sugar.
2. Remember that griseofulvin has no action against *Candida*. 

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Fig. 14.49 Pityriasis versicolor: fawn areas stand out against the untanned background.

Fig. 14.50 This patient’s holiday was spoilt by versicolor ruining her expensive tan.
CHAPTER 14  Deep fungal infections

Histoplasmosis

Histoplasma capsulatum is found in soil and in the droppings of some animals (e.g. bats). Airborne spores are inhaled and cause lung lesions, which are in many ways like those of tuberculosis. Later, granulomatous skin lesions may appear, particularly in the immunocompromised. Amphotericin B or itraconazole, given systemically, is often helpful.

Coccidioidomycosis

The causative organism, Coccidioides immitis, is present in the soil in arid areas in the USA. Its spores are inhaled, and the pulmonary infection may be accompanied by a fever. At this stage erythema nodosum (p. 101) may be seen. In a few patients the infection becomes disseminated, with ulcers or deep abscesses in the skin. Treatment is with amphotericin B or itraconazole.

Blastomycosis

Infections with Blastomyces dermatitidis are virtually confined to rural areas of the USA. Rarely, the organism is inoculated into the skin; more often it is inhaled and then spreads systemically from the pulmonary focus to other organs including the skin. There the lesions are wart-like, hyperkeratotic nodules, which spread peripherally with a verrucose edge, while tending to clear and scar centrally. Treatment is with systemic amphotericin B or itraconazole.

Sporotrichosis

The causative fungus, Sporotrichum schencki, lives saprophytically in soil or on wood in warm humid countries.

Differential diagnosis

In vitiligo (p. 246), the border is clearly defined, scaling is absent, lesions are larger, the limbs and face are often affected, and depigmentation is more complete; however, it may sometimes be hard to distinguish vitiligo from the pale non-scaly areas of treated versicolor. Seborrhoeic eczema of the trunk tends to be more erythematous, and is often confined to the presternal or interscapular areas. Pityriasis alba often affects the cheeks. Pityriasis rosea, tinea corporis, secondary syphilis and erythrasma seldom cause real confusion.

Investigations

 Scrapings, prepared and examined as for a dermatophyte infection (p. 35), show a mixture of short branched hyphae and spores (a ‘spaghetti and meatballs’ appearance). Culture is not helpful.

Treatment

A topical preparation of one of the imidazole group of antifungal drugs (Formulary 1, p. 335) can be applied at night to all affected areas for 2–4 weeks. Equally effective, but messier and more irritant, is a 2.5% selenium sulphide mixture in a detergent base (Selsun shampoo). This should be lathered on to the patches after an evening bath, and allowed to dry. Next morning it should be washed off. Three applications at weekly intervals are adequate. A shampoo containing ketoconazole is now available (Formulary 1, p. 329) and is less messy, but just as effective as the selenium ones. Alternatively, selenium sulphide lotion (USA) can be applied for 10 min, rinsed off and re-applied daily for 1 week. For widespread or stubborn infections systemic itraconazole (200 mg daily for 7 days) has been shown to be curative, but interactions with other drugs must be avoided (Formulary 2, p. 343). Recurrence is common after any treatment.

LEARNING POINTS

1 This is not a dermatophyte infection, so do not try griseofulvin or terbinafine.
2 Patients think the treatment has not worked if their pale patches do not disappear straight away—warn them about this in advance.
Infection is through a wound, where later a lesion like an indolent boil arises. Later still, nodules appear in succession along the draining lymphatics (Fig. 14.15). Potassium iodide or itraconazole are both effective.

**Actinomycosis**

The causative organism, *Actinomyces israelii*, is bacterial but traditionally considered with the fungi. It has long branching hyphae and is part of the normal flora of the mouth and bowel. In actinomycosis, a lumpy induration and scarring coexist with multiple sinuses discharging pus containing ‘sulphur granules’, made up of tangled filaments. Favourite sites are the jaw, and the chest and abdominal walls. Long-term penicillin is the treatment of choice.

**Mycetoma (Madura foot)**

Various species of fungus or actinomycetes may be involved. They gain access to the subcutaneous tissues, usually of the feet or legs, via a penetrating wound. The area becomes lumpy and distorted, later enlarging and developing multiple sinuses. Pus exuding from these shows tiny diagnostic granules. Surgery may be a valuable alternative to the often poor results of medical treatment, which is with systemic antibiotics or antifungal drugs, depending on the organism isolated.

**Further reading**


Infestations

Infestation, the presence of animal parasites on or in the body, is common in tropical countries and less so in temperate ones. Infestations fall into two main groups: 1 those caused by arthropods; and 2 those caused by worms.

**Arthropods**

Table 15.1 lists some of the ways in which arthropods affect the skin. Only a few can be discussed here.

**Insect bites**

The skin changes are partly a result of the injection of pharmacologically active substances, and partly of sensitization to injected antigens. A wheal may appear within a few minutes, to be followed by a firm itchy persistent papule, often with a central haemorrhagic punctum. Bullous reactions are common on the legs of children. The diagnosis is usually obvious; when it is not, the term papular urticaria is sometimes used.

**Papular urticaria**

**Cause**

This term, with its hint that the condition is a variant of ordinary urticaria, is a misnomer. Papular urticaria is nothing more than an excessive, possibly allergic, reaction to insect bites. The source of the bites may be simple garden pests but more often is a parasite on

<table>
<thead>
<tr>
<th>Type of arthropod</th>
<th>Manifestations</th>
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<tbody>
<tr>
<td><strong>Insects</strong></td>
<td></td>
</tr>
<tr>
<td>Hymenoptera</td>
<td>Bee and wasp stings, Ant bites</td>
</tr>
<tr>
<td>Lepidoptera</td>
<td>Caterpillar dermatitis</td>
</tr>
<tr>
<td>Coleoptera</td>
<td>Blisters from cantharidin</td>
</tr>
<tr>
<td>Diptera</td>
<td>Mosquito and midge bites, Myiasis</td>
</tr>
<tr>
<td>Aphaniptera</td>
<td>Human and animal fleas</td>
</tr>
<tr>
<td>Hemiptera</td>
<td>Bed bugs</td>
</tr>
<tr>
<td>Anoplura</td>
<td>Lice infestations</td>
</tr>
<tr>
<td><strong>Mites</strong></td>
<td></td>
</tr>
<tr>
<td>Demodex folliculorum</td>
<td>Normal inhabitant of facial hair follicles</td>
</tr>
<tr>
<td>Sarcoptes scabei</td>
<td>Human and animal scabies</td>
</tr>
<tr>
<td>Food mites</td>
<td>Grain itch, grocer’s itch, etc.</td>
</tr>
<tr>
<td>Harvest mites</td>
<td>Harvest itch</td>
</tr>
<tr>
<td>House dust mite</td>
<td>Possible role in atopic eczema</td>
</tr>
<tr>
<td>Cheyletiella</td>
<td>Papular urticaria</td>
</tr>
<tr>
<td>Ticks</td>
<td>Tick bites. Vector of rickettsial infections and erythema chronicum migrans (p. 195)</td>
</tr>
</tbody>
</table>
which burrows are the diagnostic feature. Atopic prurigo may be more difficult to distinguish but here there is usually a family history of atopy and frankly eczematous plaques are found in a typical distribution.

**Investigations**

The parents should be encouraged to act as detectives in their own environment, but some resist the idea that the lesions are caused by bites, asking why the other family members are not affected. This attitude is often supported by veterinarians who, after a superficial look at infested animals, pronounce them clear. In such cases the animal should be brushed vigorously while standing on a polythene sheet. Enough dandruff-like material can then be obtained to send to a reliable veterinary laboratory. Often the cause is a *Cheyletiella* mite infestation.

**Treatment**

Local treatment with Eurax HC ointment or calamine lotion, and the regular use of insect repellents, may be of some help but the ultimate solution is to trace the source of the bites.

Infested animals should be treated by a veterinarian, and insecticidal powders should be used for soft furnishings in the home. Sometimes professional exterminators are needed; but even measures such as these can meet with little success.

**Bed bugs (Hemiptera)**

During the day, bed bugs hide in crevices in walls and furniture; at night they can travel considerable distances to reach a sleeping person. Burning wheals, turning into firm papules, occur in groups wherever the crawling bugs have easy access to the skin, the face, neck and hands being the most common sites. Treatment should be based on the application of insecticides to walls and furniture likely to be harbouring the bugs.

**Myiasis**

The larvae of several species of fly develop only if deposited in living flesh; humans are one of several possible hosts. The skin lesions look like boils, but movement may be detected within them. The diagnosis
is proved by incising the nodule and extracting the larva.

Lice infestations (pediculosis)

Lice are flattened wingless insects that suck blood. Their eggs, attached to hairs or clothing, are known as nits. The main feature of all lice infestations is severe itching, followed by scratching and secondary infection.

Two species are obligate parasites in humans: *Pediculus humanus* (with its two varieties *P. humanus capitis*, the head louse, and *P. humanus corporis*, the body louse) and *Phthirus pubis* (the pubic louse).

Head lice

*Cause*

Head lice are still common, affecting up to 10% of children even in the smartest schools. The head louse itself measures some 3–4 mm in length and is greyish, and often rather hard to find. However, its egg cases (nits) can be seen easily enough, firmly stuck to the hair shafts. Spread from person to person is achieved by head-to-head contact, and perhaps by shared combs or hats.

*Presentation and course*

The main symptom is itching, at first around the sides and back of the scalp and then more generally over it. Scratching and secondary infection soon follow and, in heavy infestations, the hair becomes matted and smelly. Draining lymph nodes often enlarge.

*Complications*

Secondary bacterial infection may be severe enough to make the child listless and feverish.

*Differential diagnosis*

All patients with recurrent impetigo or crusted eczema on their scalps should be carefully examined for the presence of nits.

*Investigations*

None are usually required.

Body lice

*Cause*

Body louse infestations are now uncommon except in the unhygienic and socially deprived. Morphologically the body louse looks just like the head louse, but lays its eggs in the seams of clothing in contact with the skin. Transmission is via infested bedding or clothing.

*Presentation and course*

Self-neglect is usually obvious; against this background there is severe and widespread itching, especially on the trunk. The bites themselves are soon obscured by excoriations and crusts of dried blood or serum. In chronic untreated cases (“vagabond’s disease”) the skin becomes generally thickened.

Treatment

Malathion, carbaryl and permethrin preparations (Formulary 1, p. 336) are probably the treatments of choice now. They kill lice and eggs effectively; malathion has the extra value of sticking to the hair and so protecting against reinfection for 6 weeks. The policy whereby public health authorities rotate their use, with the aim of lessening the risk of resistant strains emerging, has fallen out of favour now.

Lotions should remain on the scalp for at least 12 h, and are more effective than shampoos. The application should be repeated after 1 week so that any lice that survive the first application and hatch out in that interval can be killed. Other members of the family and school mates should be checked. A toothcomb helps to remove nits but occasionally matting is so severe that the hair has to be clipped short. A systemic antibiotic may be needed to deal with severe secondary infection. Some recommend, as an alternative to the treatments mentioned above, that the hair should be combed repeatedly and meticulously with a special ‘detection comb’—but the efficacy of this method has still to be established. However, a head louse repellent, containing 2% piperonal, is available over the counter and may be worth a trial for those who are repeatedly reinfested. Systemic ivermectin therapy is reserved for infestations resisting the treatments listed above.
eczematized and pigmented; lymphadenopathy is common.

Differential diagnosis

In scabies, characteristic burrows are seen (p. 227). Other causes of chronic itchy erythroderma include eczema and lymphomas, but these are ruled out by the finding of lice and nits.

Investigations

Clothing should be examined for the presence of eggs in the inner seams.

Treatment

First and foremost treat the infested clothing and bedding. Lice and their eggs can be killed by high temperature laundering, by dry cleaning and by tumble-drying. Less competent patients will need help here. Once this has been achieved, 5% permethrin cream rinse or 1% lindane lotion (USA only) (Formulary 1, p. 335) may be used on the patient’s skin.

Pubic lice

Cause

Pubic lice (crabs) are broader than scalp and body lice, and their second and third pairs of legs are well adapted to cling on to hair. They are usually spread by sexual contact, and most commonly infest young adults.

Presentation

Severe itching in the pubic area is followed by eczematization and secondary infection. Among the excoriations will be seen small blue-grey macules of altered blood at the site of bites. The shiny translucent nits are less obvious than those of head lice (Fig. 15.2). Pubic lice spread most extensively in hairy males and may even affect the eyelashes.

Differential diagnosis

Eczema of the pubic area gives similar symptoms but lice and nits are not seen.

Fig. 15.2 Pediculosis pubis. Numerous eggs (nits) can be seen on the plucked pubic hairs.
The most dramatic part of the eruption—a excoriated, eczematized or urticarial papules—is usually on the trunk, but these changes are non-specific and a burrow has to be identified to confirm the diagnosis (Fig. 15.4).

Once on the skin, fertilized female mites burrow through the stratum corneum at the rate of about 2 mm per day, and produce two or three oval eggs each day. These turn into sexually mature mites in 2–3 weeks. The number of mites varies from case to case, from less than 10 in a clean adult to many more in an unwashed child. The generalized eruption of scabies, and its itchiness, are thought to be caused by a sensitization to the mites or their products.

Epidemiology

The prevalence of scabies in many populations rises and falls cyclically, peaking every 15–20 years. The idea of ‘herd immunity’ has been put forward to explain this, spread being most easy when a new generation of susceptible individuals has arisen.

Presentation

For the first 4–6 weeks after infestation there may be no itching, but thereafter pruritus dominates the picture, often affecting several people and being particularly severe at night.

The most dramatic part of the eruption—a excoriated, eczematized or urticarial papules—is usually on the trunk, but these changes are non-specific and a burrow has to be identified to confirm the diagnosis (Fig. 15.4).

Most burrows lie on the sides of the fingers, finger webs, sides of the hand and on the flexural aspects of the wrists. Other favourite sites include the elbows, ankles and feet (especially in infants; Fig. 15.5), nipples and genitals (Fig. 15.6). Only in infancy does scabies affect the face. Burrows are easily missed grey-white...
slightly scaly tortuous lines of up to 1 cm in length. The acarus may be seen through a lens as a small dark dot at the most recent least scaly end of the burrow. With experience it can be removed for microscopic confirmation (p. 35). On the genitals, burrows are associated with erythematous rubbery nodules (Fig. 15.7).

Course
Scabies persists indefinitely unless treated. In the chronic stage, the number of mites may be small and diagnosis is correspondingly difficult. Relapses after apparently adequate treatment are common and can be put down to reinfestation from undetected and untreated contacts.

Complications
- Secondary infection, with pustulation, is common (Fig. 15.8). Rarely, glomerulonephritis follows this.
- Repeated applications of scabicides can cause skin irritation and eczema.
- Persistent itchy red nodules may remain on the genitals or armpits of children for some months after adequate treatment.
Differential diagnosis

Only scabies shows characteristic burrows. Animal scabies from pets induces an itchy rash in humans but this lacks burrows. The lesions of papular urticaria (p. 224) are excoriated papules, in groups, mainly on the legs. Late-onset atopic eczema (p. 81), cholinergic urticaria (p. 95), lichen planus (p. 64), neurotic excoriations (p. 297) and dermatitis herpetiformis (p. 113) have their own distinctive features. Fibreglass can also cause epidemics of itching.

Investigations

With practice an acarus can be picked neatly with a needle from the end of its burrow and identified microscopically; failing this, eggs and mites can be seen microscopically in burrow scrapings mounted in potassium hydroxide (p. 35) or mineral oil. Some find dermatoscopy (p. 33) a quick and reliable way to identify the mite.

Treatment

• Use an effective scabicide; there are many on the market now (Formulary 1, p. 335). In the UK, the preferred treatment is with malathion or permethrin; lindane is no longer available. Topical treatment plus ivermectin (on a named patient basis in the UK), in a single dose of 200 µg/kg by mouth, is effective for Norwegian scabies and scabies that does not respond to topical measures alone.
• For babies over 2 months, toddlers and young children we advise permethrin cream, 25% benzyl benzoate emulsion diluted with three parts of water, or 6% precipitated sulphur in white soft paraffin (petrolatum).
• It is still not clear which scabicides can be safely used to treat pregnant women or those who are breast-feeding. Despite the absence of convincing evidence that unborn children can be damaged by topical scabicides, we prefer to use the same measures that we use to treat babies (above).
• Do not just treat the patient: treat all members of the family and sexual contacts, whether they are itching or not (Fig. 15.9).
• Have a printed sheet to give to the patient and go through it with them—scabies victims are notoriously confused.

Fig. 15.7 Unmistakable rubbery nodules on the penis, diagnostic of scabies.

Fig. 15.8 Scabies with bacterial super infection.

• Venereal disease may be acquired at the same time as scabies.
• Crusted (Norwegian) scabies, which may not be itchy, is a widespread crusted eruption in which vast numbers of mites are found. It affects people with learning difficulties or the immunosuppressed, and can be the unsuspected source of epidemics of ordinary scabies.
Parasitic worms

A textbook of tropical medicine should be consulted for more details on this subject.

Onchocerciasis

This is endemic in much of Central America and Africa where it is an important cause of blindness. The buffalo gnat (Simulium species) carries the filarial worm to humans. Infested humans become itchy with an excoriated papular eruption. Later the skin may thicken and become hyper- or hypopigmented. Dermal nodules are found, mainly near bony prominences, and contain both mature worms and microfilariae. It is the latter that invade the eye, leading to blindness. The diagnosis is confirmed by detecting active microfilariae in skin snips teased out in saline and examined microscopically. Ivermectin is now the treatment of choice. A single dose produces a prolonged reduction of microfilarial levels, and should be repeated every year until the adult worms die out. Diethylcarbamazine and suramin are now obsolete.

Filariasis

This is endemic throughout much of the tropics. The adult filarial worms, usually Wuchereria bancrofti, inhabit the lymphatics where they excite an inflammatory reaction with episodes of lymphangitis and fever, gradually leading to lymphatic obstruction and lymphoedema, usually of the legs or scrotum. Such
swellings can be massive (elephantiasis). There is an eosinophilia and microfilariae are found in the peripheral blood, mainly at night; their vector from human to human is the mosquito, in which the larvae mature. Diethylcarbamazine or ivermectin is the treatment of choice.

**Larva migrans**

The larvae of hookworms that go through their full life cycle only in cats or dogs can penetrate human skin when it is in contact with soil or sand contaminated by the faeces of these animals. The larvae move under the skin creating tortuous red itchy lines (Fig. 15.10) that advance at the rate of a few millimetres a day. The larvae do eventually die, but this can be speeded up by a single oral dose of ivermectin.

**Other worm infestations**

- Threadworm (pinworm) infestation in children can cause severe anal and vulval pruritus. The small worms are seen best at night-time when the itch is worst. Treatment is with piperazine.
- Swimmer’s itch, in tropical and lake waters, may be caused by the penetration through the skin of the cercariae of schistosomes of human and non-human origin. The skin should be towelled off immediately after swimming to prevent the schistosomes penetrating the skin as it dries.
- The larval stages of the pork tapeworm (cysticercosis) can present as multiple firm nodules in the skin.
- Larger fluctuant cysts may be caused by hydatid disease.

**Further reading**

Ultraviolet radiation (UVR) can be helpful when used to treat diseases such as psoriasis, but it can also be harmful (Fig. 16.1). It is the leading cause of skin cancers, and causes or worsens several skin disorders. UVR is non-ionizing, but changes the skin chemically by reacting with endogenous light-absorbing chemicals (chromophores), which include DNA, RNA, uronic acid and melanin. Different types of skin (now conventionally divided into six types; Table 16.1) react differently to UVR, and require different degrees of protection against the sun.

The UVR spectrum is divided into three parts (Fig. 16.2), each having different effects on the skin, although UVC does not penetrate the ozone layer of the atmosphere and is therefore currently irrelevant to skin disease. Virtually all of the UVB is absorbed in the epidermis, whereas some 30% of UVA reaches the dermis. The B wavelengths (UVB: 290–320 nm) cause sunburn and are effectively screened out by window glass. The A spectrum (UVA) is long-wave ultraviolet light, from 320 nm to the most violet colour perceptible to the eye (about 400 nm). It ages and tans the skin. The differences between the wavelengths can be recorded conveniently in the form of action spectra, which show how effective each is at producing different biological effects, such as clearing psoriasis or causing erythema.

![Fig. 16.1](https://example.com/fig16.1.png)

**Fig. 16.1** The balance between the benefits and drawbacks of sun exposure.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Always burns but never tans</td>
<td>Pale skin, red hair, freckles</td>
</tr>
<tr>
<td>II</td>
<td>Usually burns, sometimes tans</td>
<td>Fair skin</td>
</tr>
<tr>
<td>III</td>
<td>May burn, usually tans</td>
<td>Darker skin</td>
</tr>
<tr>
<td>IV</td>
<td>Rarely burns, always tans</td>
<td>Mediterranean</td>
</tr>
<tr>
<td>V</td>
<td>Moderate constitutional pigmentation</td>
<td>Latin American, Middle Eastern</td>
</tr>
<tr>
<td>VI</td>
<td>Marked constitutional pigmentation</td>
<td>Black</td>
</tr>
</tbody>
</table>

**Table 16.1** Skin types classified by their reactions to UVR.
Sunburn  

**Cause**

UVB penetrates the epidermis and superficial dermis, stimulating the production and release of prostaglandins, leukotrienes, histamine, interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α), which cause pain and redness.

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**LEARNING POINT**

Do not let your patients be hoodwinked. The drawbacks of artificial tanning far outweigh the advantages.
SKIN REACTIONS TO LIGHT

inhibitor) relieves the pain. Sprays containing benzocaine also relieve pain, but occasionally sensitize.

Phototoxicity

Basic photochemical laws require a drug to absorb UVR to cause such a reaction. Most drugs listed in Table 16.2 absorb UVA as well as UVB, and so window glass, protective against sunburn, does not protect against most phototoxic drug reactions.

Presentation and course

Skin exposed to too much UVB smart's and becomes red several hours later. Severe sunburn is painful and may blister. The redness is maximal after 1 day and then settles over the next 2 or 3 days, leaving sheet-like desquamation (Fig. 16.3), diffuse pigmentation (a ‘tan’) and, sometimes, discrete lentigines.

Differential diagnosis

Phototoxic reactions caused by drugs are like an exaggerated sunburn.

Investigations

None are required.

Treatment

The treatment is symptomatic. Baths may be cooling and oily shake lotions (e.g. oily calamine lotion), oil-in-water lotions or creams comforting. Potent topical corticosteroids (Formulary 1, p. 331) help if used early and briefly. Oral aspirin (a prostaglandin synthesis inhibitor) relieves the pain. Sprays containing benzocaine also relieve pain, but occasionally sensitize.

Phototoxicity

Basic photochemical laws require a drug to absorb UVR to cause such a reaction. Most drugs listed in Table 16.2 absorb UVA as well as UVB, and so window glass, protective against sunburn, does not protect against most phototoxic drug reactions.

Presentation and course

Tenderness and redness occur only in areas exposed both to sufficient drug and to sufficient UVR (Fig. 16.4). The signs and symptoms are those of sunburn. The skin may later develop a deep tan.

Fig. 16.3 Peeling after acute sunburn. This doctor’s son should have known better.

Fig. 16.4 Extreme photosensitivity of a patient taking griseofulvin. Note sparing of the area covered by the watch strap and ring.

Table 16.2 Drugs commonly causing photosensitivity.

<table>
<thead>
<tr>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Nalidixic acid</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Psorals</td>
</tr>
<tr>
<td>Quinidine</td>
</tr>
<tr>
<td>Sulphonamides</td>
</tr>
<tr>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
</tbody>
</table>

Fig. 16.3 Peeling after acute sunburn. This doctor’s son should have known better.
ences between phototoxicity and photoallergy are shown in Table 16.3.

**Investigations**

None are usually required. In difficult cases, phototesting can be carried out in special centres. The action spectrum (the wavelengths that cause the reaction) may incriminate a particular drug.

**Treatment**

This is the same as for sunburn. Drugs should be stopped if further exposure to ultraviolet light is likely.

**Photoallergy**

Drugs, topical or systemic, and chemicals on the skin, can interact with UVR and cause immunological reactions.

**Cause**

These reactions are not immunological. Everyone exposed to enough of the drug, and to enough UVR, will develop the reaction. Some drugs that can cause phototoxic reactions are listed in Table 16.2. In addition, contact with psoralens in plants (Fig. 16.5) can cause a localized phototoxic dermatitis (phytophotodermatitis; Fig. 16.6). These areas burn and may blister, leaving pigmentation in linear streaks and bizarre patterns.

**Differential diagnosis**

Photoallergic reactions are difficult to distinguish; the more so as the same drugs can often cause both photoallergic and phototoxic reactions. The main differ-
SKIN REACTIONS TO LIGHT

Clothing and sunscreens). Potent topical corticosteroids or a short course of a systemic corticosteroid will hasten resolution and provide symptomatic relief.

Chronic actinic dermatitis (actinic reticuloid)

Some patients with a photoallergic reaction never get over it and go on developing sun-induced eczematous areas long after the drug has been stopped.

**Complications**

Some drugs, such as the sulphonamides, can cause a persistent light reaction (see below).

**Investigations**

Photopatch testing by an expert can confirm the diagnosis. The chemical is applied for 24 h and the skin is then irradiated with UVA. An acute phototoxic contact dermatitis is then elicited. A control patch, not irradiated, rules out ordinary allergic contact dermatitis.

**Treatment**

The drug should be stopped and the patient protected from further ultraviolet exposure (avoidance, clothing and sunscreens). Potent topical corticosteroids or a short course of a systemic corticosteroid will hasten resolution and provide symptomatic relief.

**Table 16.3** Features distinguishing phototoxicity from photoallergy.

<table>
<thead>
<tr>
<th>Phototoxicity</th>
<th>Photoallergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythematous and smooth (may blister)</td>
<td>Eczematous and rough (may weep)</td>
</tr>
<tr>
<td>Immediate onset</td>
<td>Delayed onset (when immunity develops; may not occur on first exposure)</td>
</tr>
<tr>
<td>Hurts</td>
<td>Itches</td>
</tr>
<tr>
<td>Photopatch testing negative</td>
<td>Photopatch testing positive</td>
</tr>
</tbody>
</table>

**Fig. 16.7** Features distinguishing airborne allergy from photosensitivity.

to resolve when either the drug or the exposure to UVR is stopped, but this may take several weeks.

**Cause**

This is not clear but some believe minute amounts of the drug persist in the skin indefinitely.

**Presentation**

This is the same as a photoallergic reaction to a drug. The patient goes on to develop a chronic dermatitis, with thick plaques on sun-exposed areas.
Course

These patients may be exquisitely sensitive to UVR. They are usually middle-aged or elderly men who react after the slightest exposure, even through window glass or from fluorescent lights. Affected individuals also become allergic to a range of contact allergens, especially oleoresins in some plants (e.g. chrysanthemums).

Complications

None, but the persistent severe pruritic eruption can lead to depression and even suicide.

Differential diagnosis

Airborne allergic contact dermatitis may be confused, but does not require sunlight. Sometimes the diagnosis is difficult as exposure both to sunlight and to the airborne allergen occurs only out of doors. Airborne allergic contact dermatitis also affects sites which sunlight is less likely to reach, such as under the chin (Fig. 16.7). A continuing drug photoallergy, a polymorphic light eruption (see below) or eczema as a result of some other cause must also be considered.

Histology shows a dense lymphocytic infiltrate and sometimes atypical lymphocytes suggestive of a lymphoma, but the disorder seldom becomes malignant.

Investigations

Persistent light reaction can be confirmed experimentally by exposing uninvolved skin to UVA or UVB. Patch tests and photopatch tests help to distinguish between photoallergy and airborne allergic contact dermatitis, and the action spectrum may point to a certain drug. This sort of testing is difficult, and should be carried out only in specialist centres.

Treatment

Usually cared for by specialists, these patients need extreme measures to protect their skin from UVR. These include protective clothing and frequent applications of combined UVA and UVB blocking agents (Formulary 1, p. 330). Patients must protect themselves from UVR coming through windows or from fluorescent lights. Some can only go out at night. As even the most potent topical steroids are often ineffective, systemic steroids or immunosuppressants (e.g. azathioprine) may be needed for long periods.

Polymorphic light eruption

This is the most frequent cause of a so-called ‘sun allergy’.

Cause

It is speculated that UVR causes a natural body chemical to change into an allergen. Mechanisms are similar to those in drug photoallergy.

Presentation

Small itchy red papulovesicles or eczematous plaques arise from 2 h to 5 days, most commonly at 24 h, after exposure to UVR. The eruption is itchy and usually confined to sun-exposed areas (Fig. 16.8), remembering that some UVR passes through thin clothing.

Course

The disorder tends to recur each spring after UVR exposure. Tanning protects some patients so that if the initial exposures are limited, few or no symptoms occur later. Such patients can still enjoy sun exposure and outdoor activities. Others are so sensitive, or their
skin pigments so poorly, that fresh exposures continue to induce reactions throughout the summer. These patients require photoprotection, and must limit their sun exposure and outdoor activities. The rash disappears during the winter.

**Differential diagnosis**

Phototoxic reactions, photoallergic reactions, miliaria rubra, chronic actinic dermatitis, ordinary eczemas, allergic reactions to sunscreens and airborne allergic contact dermatitis should be considered.

**Investigations**

It may be possible to reproduce the dermatitis by testing non-sun-exposed skin with UVB and UVA.

**Treatment**

If normal tanning does not confer protection, sunscreens (Formulary 1, p. 330) should be used. Protective clothing, such as wide-brimmed hats, long-sleeved shirts and long trousers, is helpful. In some patients, a 4-week PUVA course (p. 59) in the late spring can create enough tan to confer protection for the rest of the season. Moderately potent topical steroids (Formulary 1, p. 331) usually improve the eruption. Hydroxychloroquine (Formulary 2, p. 351) may be effective when used over the sunny season.

**Actinic prurigo**

This is clinically distinct from a polymorphic light eruption although its unknown cause may be the same. Papules, crusts and excoriations arise on sun-exposed areas and sometimes also on other sites. Lesions may persist through the winter. It is common among North American Indians and may resemble excoriated acne, bites, eczema, erythropoietic protoporphyria or neurotic excoriations. It may be associated with atopy.

**Solar urticaria**

This is discussed in Chapter 8. Wheals occur in the sun-exposed areas, within minutes. Some patients have erythropoietic protoporphyria (p. 119) and this should be considered particularly if solar urticaria starts in infancy.

**Actinic keratoses**

These are discussed in Chapter 18.

**Actinic cheilitis**

This is discussed in Chapter 13 and see Fig. 24.14.

**Lupus erythematosus**

Many patients with lupus erythematosus (p. 119) become worse after exposure to UVR, especially to UVB. They should be warned about this, and protect themselves from the sun (avoidance, clothing and sunscreens).

**Carcinomas**

The sun can cause basal cell carcinomas, squamous cell carcinomas and malignant melanomas. These are discussed in Chapter 18.

**Exacerbated diseases**

UVR is useful in the treatment of many skin diseases, but it can also make some worse (Table 16.4).

**Porphyria cutanea tarda**

This is described in Chapter 19.

**LEARNING POINTS**

If the skin reacts badly to light through glass then:

1. Sunscreens are usually ineffective.
2. Think of drugs or porphyria.

**Cutaneous ageing**

The trouble with old skin is the way it looks rather than the way it behaves. Skin chronically damaged by UVR during childhood thereafter looks old. This ‘photoageing’ effect causes the skin to become thin on the extremities, so that it bruises and tears easily (Fig. 16.9). The elastic fibres become clumped and...
amorphous, leading clinically to a yellow pebbly look called actinic elastosis (Figs 16.10 and 16.11). Chronic exposure to sunlight, or to UVR in tanning parlours, also causes lentigines, freckles, xerosis and, of course, skin cancers. The bronzed young skins of today will become the wrinkled spotted rough prune-like ones of tomorrow.

Wrinkles occur when the dermis loses its elastic recoil, failing to snap back properly into shape. UVR damages elastic tissue and hastens this process. Although face-lifts can smooth wrinkles out, there is no way to reverse the damage fully; however, tretinoin cream (Formulary 1, p. 336) seems to help some patients. Prevention (reducing exposure to UVR) is better than any cure, and is especially important in sunny climates (Table 16.5).

Skin ages even in sun protected areas, but much more slowly. The dermis thins, skin collagen falls by about 1% per year throughout adult life, and becomes more stable (less elastic). Fibroblasts become sparser in the dermis, accounting for reduced collagen synthesis and slower wound healing.

### Table 16.4 The effect of sunlight on some skin diseases.

<table>
<thead>
<tr>
<th>Helps</th>
<th>Worsens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic eczema</td>
<td>Darier’s disease</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Parapsoriasis</td>
<td>Lupus erythematosus</td>
</tr>
<tr>
<td>Pityriasis lichenoides</td>
<td>Pellagra</td>
</tr>
<tr>
<td>Pityriasis rosea</td>
<td>Photoallergy/toxicity</td>
</tr>
<tr>
<td>Pruritus of renal failure, liver disease</td>
<td>Porphyrias (excluding acute intermittent)</td>
</tr>
<tr>
<td>AIDS</td>
<td>Xeroderma pigmentosum</td>
</tr>
</tbody>
</table>

Fig. 16.9 Thin skin on the back of the hand. The whitish areas are stellate pseudoscars, the skin having never been broken. The pseudoscars follow the dispersion of senile purpura.

Fig. 16.10 Prolonged sun exposure has caused this furrowed yellowish thickened area on the cheek (solar elastosis).

Fig. 16.11 ‘Sailor’s skin’ (cutis rhomboidalis nuchae): the deep creases on the back of the neck contain many comedones.
Table 16.5 Tips to avoid skin damage for those living in a sunny climate.

1. Apply sunscreen daily to all exposed parts—rain or shine, reapply after 20 min
2. Reapply sunscreen often when outdoors
3. Use a sunscreen with a protective factor (SPF) of at least 15
4. Wear protective clothing, including wide-brimmed hats
5. Target outdoor activities for early morning or late afternoon
6. Seek the shade
7. Avoid tanning salons
8. Do not sunbathe
9. Wear cosmetics, including lipstick
10. Help your children to protect themselves

Further reading


LEARNING POINT

If your family or patients have type I or II skin tell them that it is never too late to protect themselves from excessive sun exposure. You might be one of the few able to persuade them to think of the future.
Normal skin colour

The colour of normal skin comes from a mixture of pigments. Untanned Caucasoid skin is pink, from oxyhaemoglobin in the blood within the papillary loops and superficial horizontal plexus (see Fig. 2.10). Melanin (see below) blends with this colour, e.g. after a suntan. Melanin is, of course, also responsible for the shades of brown seen in Negroid skin. Other hues are caused by the addition to these pigments of yellow from carotene, found mainly in subcutaneous fat and in the horny layer of the epidermis. There is no natural blue pigment: when blue is seen it is either because of an optical effect from normal pigment (usually melanin) in the dermis, or the presence of an abnormal pigment.

Melanogenesis

Tyrosine, formed in the liver by hydroxylation of the essential amino acid phenylalanine under the influence of phenylalanine hydroxylase, is the substrate for the reactions that occur in melanocytes (Fig. 17.1). These are the only cells in the epidermis to contain tyrosinase (dopa oxidase), the rate-limiting enzyme in melanogenesis. This copper-dependent enzyme converts tyrosine to melanin. Dopa is formed by the oxidation of tyrosine, and further enzymic action leads to the formation of dopaquinone. Eumelanins, brown or black pigments, are then formed by polymerization. Phaeomelanins and trichochromes, the pigments in red hair, are synthesized in a similar way, except that cysteine reacts with dopaquinone and is incorporated.

Fig. 17.1 The control of melanogenesis. Melanocortin 1 receptor (MC1R) activity is both constitutive and rate limiting when promoting melanogenesis, via cyclic adenosine monophosphate (cAMP) production and tyrosinase stimulation. The MC1R is activated by ligands such as α-melanocyte-stimulating hormone (α-MSH) and other pituitary peptides. In the absence of such ligands or the MC1R itself (knockout animals), and with loss-of-function mutations of the MC1R, phaeomelanin is produced. The precise mechanism by which ultraviolet radiation stimulates melanogenesis remains uncertain.
into the subsequent polymers. Phaeomelanins and eumelanins may intermesh to form mixed melanin polymers.

Eumelanins and phaeomelanins differ from neuro-melanins, the pigments found in the substantia nigra and in cells of the chromaffin system (adrenal medulla, sympathetic ganglia, etc.). The latter are derived from tyrosine using a different enzyme, tyrosine hydroxylase, which is not found in melanocytes.

Melanin is made within melanosomes, tiny particles measuring about $0.1 \times 0.7$ µm, shaped either like American footballs (eumelanosomes, containing eumelanin) or British soccer balls (phaeomelanosomes, containing phaeomelanin). Eventually, fully melanized melanosomes pass into the dendritic processes of the melanocyte to be injected into neighbouring keratinocytes. Once there, the melanosomes are engulfed in lysosomal packages (melanosome complexes) and distributed throughout the cytoplasm.

Negroids are not black because they have more melanocytes than Caucasoids, but because their melanocytes produce more and larger melanosomes, which are broken down less rapidly in the melanosome complexes. Melanins protect against ultraviolet radiation (UVR) damage by absorbing and scattering the rays, and by scavenging free radicals.

**The control of melanogenesis**

Melanogenesis can be increased by several stimuli, the most important of which is UVR. Tanning involves two distinct reactions.

1. An immediate reaction occurs within 5 min of exposure to long-wave ultraviolet (UVA: 320–400 nm) and may be because of the photo-oxidation of preformed melanin. This pigment-darkening reaction, which lasts about 15 min, is responsible for the well-known phenomenon of a ‘false tan’.

2. The production of new pigment is delayed for some 24 h after exposure to medium wave ultraviolet (UVB: 290–320 nm) and UVA. It depends on the proliferation of melanocytes, an increase in tyrosinase activity and melanosome production, and an increased transfer of new melanosomes to their surrounding keratinocytes.

A neat control mechanism involving glutathione has been postulated. Reduced glutathione in the epidermis, produced by the action of glutathione reductase on glutathione, inhibits tyrosinase. UVR and some inflammatory skin conditions may induce pigmentation by oxidizing glutathione and so blocking its inhibition of melanogenesis.

Melanocytes are also influenced by melanocyte-stimulating hormone (MSH; peptides from the pituitary and other areas of the brain) (Fig. 17.1). Their melanocyte-stimulating activity is caused by a common heptapeptide sequence, cleaved from the precursor protein, pro-opiomelanocortin, as a result of two proconvertase enzymes. However, MSH peptides may play little part in the physiological control of pigmentation. Hypophysectomy will not cause a black skin to lighten and only large doses of adrenocorticotrophic hormone (ACTH), in pathological states (see below), will increase skin pigmentation. It is now known that pro-opiomelanocortin and MSH peptides are also produced by both keratinocytes and melanocytes in the skin; so MSH may have a paracrine or autocrine function. In the skin, α-MSH also acts as an anti-inflammatory agent by antagonizing the effects of interleukin 1 (IL-1) in inducing IL-2 receptors on lymphocytes (p. 12) and in inducing pyrexia.

Animal experiments indicate that oestrogens, progestogens and, possibly, testosterone may, in some circumstances, stimulate melanogenesis, either directly or by increasing the release of MSH peptides from the pituitary.

**Genetics and skin pigmentation**

Genetic differences determine the pigmentation of the different races. The black person living in Britain, and the white person living in Africa remain black and white, respectively. None the less, there is some phenotypic variation in skin colour, e.g. tanning after sun exposure. Recently, red hair has been shown to be a result of genetic variations in the amino acid sequence of the melanocortin 1 receptor (MC1R) (Fig. 17.1). Some genodermatoses with abnormal pigmentation are described in Chapter 21.

**Abnormal skin colours**

These may be caused by an imbalance of the normal pigments mentioned above (e.g. in cyanosis, chloasma and carotenaemia) or by the presence of abnormal pigments (Table 17.1). Sometimes it is difficult to distinguish between the colours of these pigments; e.g.
Oculocutaneous albinism
In this condition, little or no melanin is made either in the skin and eyes (oculocutaneous albinism) or in the eyes alone (ocular albinism) not discussed further here. The prevalence of albinism of all types ranges from 1 in 20,000 in the USA and UK to 5% in some communities.

Cause
The hair bulb test (see Investigations) separates oculocutaneous albinism into two main types: tyrosinase-negative and tyrosinase-positive. Roughly
equal numbers of the two types are found in most communities, both being inherited as autosomal recessive traits. This explains how children with two albino parents can sometimes themselves be normally pigmented, the genes being complementary in the double heterozygote (Fig. 17.3).

The tyrosinase gene lies on chromosome 11q14-q21. More than 20 allelic variations have been found there in patients with tyrosinase-negative albinism. The gene for tyrosinase-positive human albinism has been mapped to chromosome 15q11-q13. It probably encodes for an ion channel protein in the melanosome involved in the transport of tyrosine.

**Presentation and course**

The whole skin is white and pigment is also lacking in the hair, iris and retina (Fig. 17.3). Albinos have poor sight, photophobia and a rotatory nystagmus. As they grow older tyrosinase-positive albinos gain a little pigment in their skin, iris and hair. Negroid skin becomes yellow-brown and the hair becomes yellow. Albinos may also develop freckles. Sunburn is common on unprotected skin. As melanocytes are present, albinos have non-pigmented melanocytic naevi and may develop amelanotic malignant melanomas.

**Complications**

In the tropics these unfortunate individuals develop numerous sun-induced skin tumours even when they are young, confirming the protective role of melanin.

**Differential diagnosis**

Piebaldism and vitiligo are described below.

**Investigations**

Prenatal diagnosis of albinism is now possible but may not be justifiable in view of the good prognosis. A biopsy from fetal skin, taken at 20 weeks, is examined by electron microscopy for arrested melanosome development.

The hair bulb test, in which plucked hairs are incubated in dihydroxyphenylalanine, distinguishes tyrosinase-positive from tyrosinase-negative types. Those whose hair bulbs turn black (tyrosine-positive) are less severely affected.
Vitiligo

The word vitiligo comes from the Latin word *vitellus*, which means ‘veal’ (pale, pink flesh). It is an acquired circumscribed depigmentation, found in all races; its prevalence may be as high as 0.5–1%; its inheritance is polygenic.

**Cause and types**

There is a complete loss of melanocytes from affected areas. There are two main patterns: a common generalized one and a rare segmental type. *Generalized vitiligo*, including the acrofacial variant, usually starts after the second decade. There is a family history in 30% of patients and this type is most frequent in those with autoimmune diseases such as diabetes, thyroid disorders and pernicious anaemia. It is postulated that in this type melanocytes are the target of a cell-mediated autoimmune attack.

*Segmental vitiligo* is restricted to one part of the body, but not necessarily to a dermatome. It occurs earlier than generalized vitiligo, and is not associated with autoimmune diseases. Trauma and sunburn can precipitate both types.

**Clinical course**

*Generalized type*. The sharply defined, usually symmetrical (Fig. 17.4), white patches are especially common on the backs of the hands, wrists, fronts of knees, neck and around body orifices. The hair of the scalp and beard may depigment too. In Caucasoids, the surrounding skin is sometimes hyperpigmented.

The course is unpredictable: lesions may remain static or spread; occasionally they repigment spontaneously from the hair follicles.

*Segmental type*. The individual areas look like the generalized type but their segmental distribution is striking. Spontaneous repigmentation occurs more often in this type than in generalized vitiligo (Fig. 17.5).

**Differential diagnosis**

Contact with depigmenting chemicals, such as hydroquinones and substituted phenols in the rubber industry, should be excluded. Pityriasis versicolor (p. 221) must be considered; its fine scaling and less
diseases that cause patchy hypopigmentation are leishmaniasis (p. 201), yaws (p. 195) and pinta.

Treatment

Treatment is unsatisfactory. Recent patches may respond to a potent or very potent topical steroid, applied for 1–2 months. After this, the strength should be gradually tapered to a mildly potent steroid for maintenance treatment. Some patients improve with psoralesns (trimethylpsoralen or 8-methoxypsoralen, in a dosage of 0.4–0.6 mg/kg body weight), taken 1–2 h before graduated exposure to natural sunshine or to artificial UVA (PUVA; p. 59). Narrow band (311 nm) UVB may also be effective. Therapy is given 2–3 times weekly for at least 6 months; new lesions seem to respond best. Autologous skin grafts are becoming popular in some centres although they remain experimental. The two most common procedures are minigrafting (implants of 1 mm grafts from unaffected skin) and suction blister grafting (using the epidermal roofs of suction blisters from unaffected skin for grafting). Melanocyte and stem cell transplants, in which single cell suspensions are made from unaffected skin and applied to dermabraded vitiliginous skin, are also being investigated. The use of these techniques may be limited by cost, and by the development of vitiligo (Köbner phenomenon) at donor sites.

As a general rule, established vitiligo is best left untreated in most white people, although advice about suitable camouflage preparations (Formulary 1, p. 330) to cover unsightly patches should be given. Sun avoidance and screening preparations (Formulary 1, p. 330) are needed to avoid sunburn of the affected areas and a heightened contrast between the pale and dark areas. Black patients with extensive vitiligo can be completely and irreversibly depigmented by creams containing the monobenzyl ether of hydroquinone.

Fig. 17.4 Striking patchy vitiligo on the knees.

Fig. 17.5 Vitiligo: patchy repigmentation is caused by the migration of melanocytes from the depths of the hair follicles.

LEARNING POINTS

1. Vitiligo looks ugly and sunburns easily. Treat with cosmetic cover and sunscreens or sun avoidance.
2. Do not promise a cure.
Disorders with increased pigmentation (hypermelanosis)

Some of these disorders are listed in Table 17.3. The most common will be described below and the mechanisms involved are summarized in Fig. 17.7.

Table 17.3 Some causes of hyperpigmentation.

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Freckles</th>
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<tr>
<td></td>
<td>Lentigines</td>
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<tr>
<td></td>
<td>Café au lait macules</td>
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<td>Peutz–Jeghers syndrome</td>
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<td></td>
<td>Xeroderma pigmentosum (Chapter 21)</td>
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<td></td>
<td>Albright’s syndrome: segmental hyperpigmentation, fibrous dysplasia of bones, precocious puberty</td>
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<tr>
<td>Endocrine</td>
<td>Addison’s disease</td>
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<td>Cushing’s syndrome</td>
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<td>Pregnancy</td>
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<td>Renal failure</td>
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<td>Metabolic</td>
<td>Biliary cirrhosis</td>
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<td>Haemochromatosis</td>
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<td>Porphyria</td>
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<td>Nutritional</td>
<td>Malabsorption</td>
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<td>Carcinomatosis</td>
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<td>Kwashiorkor</td>
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<td>Pellagra</td>
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<td>Drugs</td>
<td>Photosensitizing drugs</td>
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<td>ACTH and synthetic analogues</td>
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<td>Oestrogens and progestogens</td>
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<td>Psoralens</td>
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<td>Busulfan</td>
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<td>Minocycline</td>
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<td>Postinflammatory</td>
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<td>Eczema</td>
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<td>Secondary syphilis</td>
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<td>Systemic sclerosis</td>
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<td>Lichen and macular amyloidosis</td>
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<td></td>
<td>Cryotherapy</td>
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<tr>
<td>Poikiloderma</td>
<td>Acanthosis nigricans (p. 283)</td>
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<td></td>
<td>Pigmented naevi (p. 257)</td>
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<td></td>
<td>Malignant melanoma (p. 268)</td>
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<td></td>
<td>Mastocytosis (p. 279)</td>
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</table>

ACTH, adenocorticotrophic hormone.

The social implications of this must be discussed and carefully considered, and written consent given before such treatment is undertaken.

Postinflammatory depigmentation

This may follow eczema, psoriasis, sarcoidosis, lupus erythematosus and, rarely, lichen planus. It may also result from cryotherapy or a burn. In general, the more severe the inflammation, the more likely pigment is to decrease rather than increase in its wake. These problems are most significant in Negroids or Asians. With time, the skin usually repigments. Pityriasis alba is common on the faces of children. The initial lesion is probably a variant of eczema (pinkish with fine scaling), which fades leaving one or more pale, slightly scaly, areas (Fig. 17.6). Exposure to the sun makes the patches more obvious.

White hair

Melanocytes in hair bulbs become less active with age and white hair (canities) is a universal sign of ageing. Early greying of the hair is seen in the rare premature ageing syndromes, such as Werner’s syndrome, and in autoimmune conditions such as pernicious anaemia, thyroid disorders and Addison’s disease.
Lentigo

Simple and senile lentigines look alike. They are light or dark brown macules, ranging from 1 mm to 1 cm across. Although usually discrete, they may have an irregular outline. Simple lentigines arise most often in childhood as a few scattered lesions, often on areas not exposed to sun, including the mucous membranes. Senile or solar lentigines are common after middle age on the backs of the hands (‘liver spots’; Fig. 17.10) and on the face (Fig. 17.11). In contrast to freckles, lentigines have increased numbers of melanocytes. They should be distinguished from freckles, from junctional melanocytic naevi (p. 258) and from a lentigo maligna (p. 271). Treatment is usually unnecessary but melanin-specific high energy lasers (e.g. pigmented lesion dye laser, 510 nm; Q-switched ruby laser, 694 nm; Q-switched alexandrite laser, 755 nm) are extremely

Freckles (ephelides)

Freckles are so common that to describe them seems unnecessary. They are seen most often in the red-haired or blond person as sharply demarcated light brown-ginger macules, usually less than 5 mm in diameter. They multiply and become darker with sun exposure.

Increased melanin is seen in the basal layer of the epidermis without any increase in the number of melanocytes, and without elongation of the rete ridges (Fig. 17.8). No treatment is necessary.

Melanotic macule of the lip

This common lesion (Fig. 17.9) worries doctors but is benign. Its histology is similar to that of a freckle (Fig. 17.8).
CHAPTER 17

Effective for treating ugly lesions. Liver spots associated with actinic damage lighten or clear with the daily application of 0.1% tretinoin cream (Formulary 1, p. 336) or 3% hydroquinone (Formulary 1, p. 330).

Conditions associated with multiple lentigines

Three rare but striking syndromes feature multiple lentigines.

Peutz–Jeghers syndrome

Profuse lentigines are seen on and around the lips in this autosomal dominant condition (Fig. 17.12). Scattered lentigines also occur on the buccal mucosa, gums, hard palate, hands and feet. The syndrome is important because of its association with polyposis of the small intestine, which may lead to recurrent intussusception and, rarely, to malignant transformation of the polyps. Ten per cent of affected women have ovarian tumours.

Cronkhite–Canada syndrome

This consists of multiple lentigines on the backs of the hands and a more diffuse pigmentation of the palms and volar aspects of the fingers. It may also associate with gastrointestinal polyposis. Alopecia and nail abnormalities complete the rare but characteristic clinical picture.

LEOPARD syndrome

This is an acronym for generalized Lentiginosis associated with cardiac abnormalities demonstrated by ECG,
obvious during the summer and will minimize the chance of spread.

**Endocrine hyperpigmentation**

**Addison’s disease**

Hyperpigmentation caused by the overproduction of ACTH is often striking. It may be generalized or limited to the skin folds, creases of the palms, scars and the buccal mucosa.

**Cushing’s syndrome**

Increased ACTH production may cause a picture like that of Addison’s disease. The hyperpigmentation may become even more marked after adrenalectomy (Nelson’s syndrome).

**Pregnancy**

There is a generalized increase in pigmentation during pregnancy, especially of the nipples and areolae, and of the linea alba. Chloasma (see above) may also occur. The nipples and areolae remain pigmented after parturition.

**Chronic renal failure**

The hyperpigmentation of chronic renal failure and of patients on haemodialysis is caused by an increase in levels of pituitary melanotrophic peptides, normally cleared by the kidney.

**Porphyria**

Formed porphyrins, especially uroporphyrins, are produced in excess in cutaneous hepatic porphyria and congenital erythropoietic porphyria (p. 287). These endogenous photosensitizers induce hyperpigmentation on exposed areas; skin fragility, blistering, milia and hypertrichosis are equally important clues to the diagnosis.

**Nutritional hyperpigmentation**

Any severe wasting disease, such as malabsorption, AIDS, tuberculosis or cancer, may be accompanied by diffuse hyperpigmentation. Kwashiorkor presents a
Busulfan and bleomycin, used to treat some forms of leukaemia, frequently cause diffuse hyperpigmentation but may also cause brown streaks (flagellate hyperpigmentation). Minocycline can leave blue-black drug deposits in inflamed acne spots on the shins or on the mucosae. They can be removed successfully with Q-switched ruby laser (694 nm) treatment.

**Postinflammatory hyperpigmentation**

This is common after lichen planus (p. 64). It is also a feature of systemic sclerosis (p. 126) and some types of cutaneous amyloidosis, and is often an unwelcome sequel of cryotherapy.

**Poikiloderma**

Poikiloderma is the name given to a triad of signs: reticulate pigmentation, atrophy and telangiectasia. It is not a disease but a reaction pattern with many causes including X-irradiation, photocontact reactions, and connective tissue and lymphoreticular disorders. Congenital variants (Rothmund–Thomson syndrome, Bloom’s syndrome and Cockayne’s syndrome) associated with photosensitivity, dwarfism and mental retardation also occur.

**Further reading**


This chapter deals both with skin tumours arising from the epidermis and its appendages, and from the dermis (Table 18.1).

**Prevention**

Many skin tumours (e.g. actinic keratoses, lentigines, keratoacanthomas, basal cell carcinomas, squamous cell carcinomas, malignant melanomas and, arguably, acquired melanocytic naevi) would all become less common if Caucasoids, especially those with a fair skin, protected themselves adequately against sunlight. The education of those living in sunny climates or holidaying in the sun has already reaped great rewards here (Fig. 18.1). Successful campaigns have focused on regular self-examination and on reducing sun exposure by avoidance, clothing and sunscreen preparations (Figs 18.2 and 18.3). Public compliance has been encouraged by imaginative slogans like the Australian ‘sun smart’ and ‘slip, slap and slop’ (slip on the shirt, slap on the hat and slop on the sunscreen) advice, the

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<table>
<thead>
<tr>
<th>Derived from</th>
<th>Benign</th>
<th>Premalignant/carcinoma in situ</th>
<th>Malignant</th>
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<tbody>
<tr>
<td>Epidermis and appendages</td>
<td>Viral wart</td>
<td>Keratoacanthoma</td>
<td>Basal cell carcinoma</td>
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<td>Squamous cell papilloma</td>
<td>Intraepidermal carcinoma</td>
<td>Squamous cell carcinoma</td>
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<td>Seborrhoeic keratosis</td>
<td>Actinic keratosis</td>
<td>Malignant melanoma</td>
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<tr>
<td></td>
<td>Skin tag</td>
<td>Sebaceous naevus</td>
<td>Paget’s disease of the nipple (although, strictly, a breast tumour)</td>
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<tr>
<td></td>
<td>Linear epidermal naevus</td>
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<td>Milium</td>
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<td>Melanocytic naevus</td>
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<td>Epidermoid/pilar cyst</td>
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<td>Chondrodermatitis nodularis helics (although, strictly, an inflammation)</td>
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<td>Dermis</td>
<td>Haemangioma</td>
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<td>Kaposi’s sarcoma</td>
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<td>Lymphangioma</td>
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<td>Lymphoma</td>
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<td>Glomus tumour</td>
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<td>Dermatofibrosarcoma protuberans</td>
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<td>Pyogenic granuloma</td>
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<td>Metastases</td>
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<td>Dermatofibroma</td>
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<td>Lipoma</td>
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<td></td>
<td>Lymphocytoma cutis</td>
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<td>Mastocytosis</td>
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Table 18.1 Skin tumours.
American Academy of Dermatology ‘ABCs’ (away, block, cover up, shade) leaflet and that lovable American creature Joel Mole.

Tumours of the epidermis and its appendages

Benign

Viral warts

These are discussed in Chapter 13, but are mentioned here for two reasons: first, solitary warts are sometimes misdiagnosed on the face or hands of the elderly; and, secondly, a wart is one of the few tumours in humans that is, without doubt, caused by a virus. Seventy per cent of transplant patients who have been immunosuppressed for over 5 years have multiple viral warts and there is growing evidence that immunosuppression, viral warts and ultraviolet radiation interact in this setting to cause squamous cell carcinoma (p. 267).

Squamous cell papilloma

This common tumour, arising from keratinocytes, may resemble a viral wart clinically. Sometimes an excessive hyperkeratosis produces a horn-shaped excrescence (a ‘cutaneous horn’). Excision, or curet-
SKIN TUMOURS

• colour varies from yellow to dark brown; and
• surface may have greasy scaling and scattered keratin plugs (‘currant bun’ appearance).

Clinical course
Lesions may multiply with age but remain benign.

Differential diagnosis
Seborrhoeic keratoses are easily recognized. Occasionally they can be confused with a pigmented cellular naevus, a pigmented basal cell carcinoma and, most importantly, with a malignant melanoma. Some Afro-Caribbeans have many dark warty papules on their faces (dermatosis papulosa nigra; Fig. 18.6). Histologically these are like seborrhoeic warts.

Seborrhoeic keratosis (basal cell papilloma, seborrhoeic wart)
This is a common benign epidermal tumour, unrelated to sebaceous glands. The term ‘senile wart’ should be avoided as it offends many patients.

Cause
Usually unexplained but:
• multiple lesions may be inherited (autosomal dominant);
• occasionally follow an inflammatory dermatosis; or
• very rarely, the sudden eruption of hundreds of itchy lesions is associated with an internal neoplasm (Leser–Trélat sign).

Presentation
Seborrhoeic keratoses usually arise after the age of 50 years, but flat inconspicuous lesions are often visible earlier. They are often multiple (Figs 18.4 and 18.5) but may be single. Lesions are most common on the face and trunk. The sexes are equally affected.

Physical signs:
• a distinctive ‘stuck-on’ appearance;
• may be flat, raised or pedunculated;
• colour varies from yellow to dark brown; and
• surface may have greasy scaling and scattered keratin plugs (‘currant bun’ appearance).

Clinical course
Lesions may multiply with age but remain benign.

Differential diagnosis
Seborrhoeic keratoses are easily recognized. Occasionally they can be confused with a pigmented cellular naevus, a pigmented basal cell carcinoma and, most importantly, with a malignant melanoma. Some Afro-Caribbeans have many dark warty papules on their faces (dermatosis papulosa nigra; Fig. 18.6). Histologically these are like seborrhoeic warts.
Skin tags occur around the neck and within the major flexures. They look unsightly and may catch on clothing and jewellery. They are soft skin-coloured or pigmented pedunculated papules (Fig. 18.8).

Differential diagnosis

The appearance is unmistakable. Tags are rarely confused with small melanocytic naevi.

Treatment

Small lesions can be snipped off with fine scissors, frozen with liquid nitrogen, or destroyed with a hyfrecator without local anaesthesia. There is no way of preventing new ones from developing.

Investigations

Biopsy is needed only in rare dubious cases. The histology is diagnostic (Fig. 18.7): the lesion lies above the general level of the surrounding epidermis and consists of proliferating basal cells and horn cysts.

Treatment

Seborrhoeic keratoses can safely be left alone, but ugly or easily traumatized ones can be removed with a curette under local anaesthetic (this has the advantage of providing histology), or by cryotherapy.

LEARNING POINT

If you cannot tell most seborrhoeic warts from a melanoma you will send too many elderly people unnecessarily to the pigmented lesion clinic.

Skin tags (acrochordon)

These common benign outgrowths of skin affect mainly the middle-aged and elderly.

Cause

This is unknown but the trait is sometimes familial. Skin tags are most common in obese women, and rarely are associated with tuberous sclerosis (p. 302), acanthosis nigricans (p. 383) or acromegaly, and diabetes.
Skin Tumours

With the exception of congenital melanocytic naevi (see below), most appear in early childhood, often with a sharp increase in numbers during adolescence. Further crops may appear during pregnancy, oestrogen therapy or, rarely, after cytotoxic chemotherapy and immunosuppression, but new lesions come up less often after the age of 20 years.

Melanocytic naevi in childhood are usually of the ‘junctional’ type, with proliferating melanocytes in clumps at the dermo-epidermal junction. Later, the melanocytes round off and ‘drop’ into the dermis. A ‘compound’ naevus has both dermal and junctional components. With maturation the junctional component disappears so that the melanocytes in an ‘intradermal’ naevus are all in the dermis (Fig. 18.10).

Table 18.2 Classification of melanocytic naevi.

<table>
<thead>
<tr>
<th>Congenital melanocytic naevi</th>
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<tr>
<td>Acquired melanocytic naevi</td>
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<tr>
<td>Junctional naevus</td>
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<tr>
<td>Compound naevus</td>
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<tr>
<td>Intradermal naevus</td>
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<tr>
<td>Spitz naevus</td>
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<tr>
<td>Blue naevus</td>
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<tr>
<td>Atypical melanocytic naevus</td>
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</table>

With the exception of congenital melanocytic naevi (see below), most appear in early childhood, often with a sharp increase in numbers during adolescence. Further crops may appear during pregnancy, oestrogen therapy or, rarely, after cytotoxic chemotherapy and immunosuppression, but new lesions come up less often after the age of 20 years.

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Presentation

**Congenital melanocytic naevi** (Figs 18.11 and 18.12). These are present at birth or appear in the neonatal period and are seldom less than 1 cm in diameter. Their colour varies from brown to black or blue-black. With maturity some become protuberant
CHAPTER 18

Junctional melanocytic naevi (Fig. 18.13). These are roughly circular macules. Their colour ranges from mid to dark brown and may vary even within a single lesion. Most naevi of the palms, soles and genitals are of this type.

Compound melanocytic naevi (Fig. 18.14). These are domed pigmented nodules of up to 1 cm in diameter. They may be light or dark brown but their colour is more even than that of junctional naevi. Most are smooth, but larger ones may be cerebriform, or even hyperkeratotic and papillomatous; many bear hairs.

Fig. 18.11 Congenital melanocytic naevus.

Fig. 18.12 A large hairy congenital melanocytic naevus. (Courtesy of Dr Auf Qaba, St John’s Hospital, Livingstone.)

and hairy, with a cerebriform surface. Such lesions can be disfiguring, e.g. a ‘bathing trunk’ naevus, and carry an increased risk of malignant transformation.

Fig. 18.13 Junctional melanocytic naevus.

Fig. 18.14 Compound melanocytic naevus. No recent change.
appear in childhood and adolescence, on the limbs, buttocks and lower back. They are usually solitary.

Mongolian spots. Pigment in dermal melanocytes is responsible for these bruise-like greyish areas seen on the lumbosacral area of most Down’s syndrome and many Asian and black babies. They usually fade during childhood.

Atypical mole syndrome (dysplastic naevus syndrome; Fig. 18.18). Clinically atypical melanocytic naevi can

Fig. 18.15 Intradermal melanocytic naevus with numerous shaved hairs.

Fig. 18.16 Spitz naevus.

Intradermal melanocytic naevi (Fig. 18.15). These look like compound naevi but are less pigmented and often skin-coloured.

Spitz naevi (juvenile melanomas; Fig. 18.16). These are usually found in children. They develop over a month or two as solitary pink or red nodules of up to 1 cm in diameter and are most common on the face and legs. Although benign, they are often excised because of their rapid growth.

Blue naevi (Fig. 18.17). So-called because of their striking slate grey-blue colour, blue naevi usually

Fig. 18.17 The blue ink matches the blue naevus.

Fig. 18.18 Atypical moles in a 12-year-old girl. Note the malignant melanoma lying between the scapulae.
may be seen. A Spitz naevus has a histology worry-
ingly similar to that of a melanoma. It shows dermal
oedema and dilatated capillaries, and is composed
of large epithelioid and spindle-shaped naevus cells,
some of which may be in mitosis.

In a blue naevus, naevus cells are seen in the mid
and deep dermis.

The main features of clinically atypical (‘dysplastic’)
naevi are lengthening and bridging of rete ridges, and
the presence of junctional nests showing melanocytic
dysplasia (nuclear pleomorphism and hyperchroma-
tism). Fibrosis of the papillary dermis and a lympho-
cytic inflammatory response are also seen.

Complications

• Inflammation. Pain and swelling are common but
are not features of malignant transformation. They
are caused by trauma, bacterial folliculitis or a foreign
body reaction to hair after shaving or plucking.

• Depigmented halo (Fig. 18.19). So-called ‘halo naevi’
are uncommon but benign. There may be vitiligo
elsewhere. The naevus in the centre often involutes
spontaneously before the halo repigments.

• Malignant change. This is extremely rare except
in congenital melanocytic naevi, where the risk has

Differential diagnosis of melanocytic naevi

• Malignant melanomas. This is the most important
part of the differential diagnosis. Melanomas are
very rare before puberty, single and more variably
pigmented and irregularly shaped (other features are
listed below under Complications).

• Seborrhoeic keratoses. These can cause confusion
in adults but have a stuck-on appearance and are
warty. Tell-tale keratin plugs and horny cysts may be
seen with the help of a lens.

• Lentigines. These may be found on any part of the
skin and mucous membranes. More profuse than
junctional naevi, they are usually grey-brown rather
than black, and develop more often after adolescence.

• Ephelides (freckles). These are tan macules less than
5 mm in diameter. They are confined to sun-exposed
areas, being most common in blond or red-haired
people.

• Haemangiomas. Benign proliferations of blood
vessels, including haemangiomas and pyogenic gran-
ulomas, may be confused with a vascular Spitz naevus
or an amelanotic melanoma.

Histology

Most acquired lesions fit into the scheme given in
Fig. 18.10: orderly nests of benign naevus cells are
seen in the junctional region, in the dermis, or in both.
However, some types of melanocytic naevi have their
own distinguishing features. In congenital naevi the
naevus cells may extend to the subcutaneous fat, and
hyperplasia of other skin components (e.g. hair follicles)
Epidermoid and pilar cysts

Often incorrectly called ‘sebaceous cysts’, these are common and can occur on the scalp, face, behind the ears and on the trunk. They often have a central punctum; when they rupture, or are squeezed, foul-smelling cheesy material comes out. Histologically, the lining of a cyst resembles normal epidermis (an epidermoid cyst) or the outer root sheath of the hair follicle (a pilar cyst). Occasionally an adjacent foreign body reaction is noted. Treatment is by excision, or by incision followed by expression of the contents and removal of the cyst wall.

Milia

Milia are small subepidermal keratin cysts (Fig. 18.21). They are common on the face in all age groups and appear as tiny white millet seed-like papules of from 0.5 to 2 mm in diameter. They are occasionally seen at the site of a previous subepidermal blister (e.g. in epidermolysis bullosa and porphyria cutanea tarda). The contents of milia can be picked out with a sterile needle without local anaesthesia.

Table 18.3 The ABCDE of malignant melanoma.

<table>
<thead>
<tr>
<th>Asymmetry</th>
<th>Border irregularity</th>
<th>Colour variability</th>
<th>Diameter greater than 0.5 cm</th>
<th>Elevation irregularity</th>
</tr>
</thead>
</table>

Even if you think it is harmless, do not be afraid to refer a mole that has changed to a dermatologist.

Fig. 18.20 Malignant melanoma developing within a congenital melanocytic naevus.

Fig. 18.21 Milia.
Clinical features

They occur mainly on the exposed skin of fair individuals. More than two-thirds are on the face and most of the rest are on the arms. The lesion starts as a pink papule that rapidly enlarges; it may reach a diameter of 1 cm in a month or two. After 5 or 6 weeks the centre of the nodule forms either a keratinous plug or a crater (Fig. 18.23). If left, the lesion often resolves spontaneously over 6–12 months but leaves an ugly depressed scar.

Differential diagnosis

Squamous cell carcinoma is the main tumour to be distinguished from a keratoacanthoma. However, carcinomas grow more slowly and usually lack symmetry.

Histology

It is not possible to tell a keratoacanthoma from a squamous cell carcinoma histologically unless the architecture of the whole lesion can be assessed, including its base (Fig. 18.24). A typical lesion is symmetrical and composed of proliferating fronds...
of epidermis that show mitotic activity but retain a well-differentiated squamous appearance with the production of much 'glassy' keratin. The centre of the cup-shaped mass is filled with keratin.

**Treatment**

Excision or curettage and cautery are both effective. Occasionally, a further curetting may be needed but this should be performed only once; if this is still ineffective, the lesion must be excised.

**Intraepidermal carcinoma (Bowen’s disease)**

Usually single, these slowly expanding pink scaly plaques (Fig. 18.25) take years to reach a diameter of a few centimetres. Their border is sharply defined, with reniform projections and notches. About 3% progress into an invasive squamous cell carcinoma. The presence of several may be a clue to previous exposure to carcinogens (e.g. excessive sun exposure, arsenic in a tonic when young).

**Differential diagnosis**

An intraepidermal carcinoma is often mistaken for psoriasis (Chapter 5), discoid eczema (p. 89), superficial basal cell carcinoma (see below) or for Paget’s disease in the peri-anal region.

**Treatment**

These lesions are unaffected by local steroids. Small lesions may occasionally be left under observation in the frail and elderly. Cryotherapy or curettage are the treatments of choice for small lesions on a site where healing should be good (e.g. face or trunk); excision is an alternative. Photodynamic therapy (p. 325) is useful for large lesions on a poor healing site (e.g. the lower legs of the elderly). Topical 5-fluorouracil or imiquimod is helpful for multiple lesions (see Guidelines in Further reading).

**Actinic keratoses**

These discrete rough-surfaced lesions crop up on sun-damaged skin. They are premalignant, although only a few turn into a squamous cell carcinoma.

**Cause**

The effects of sun exposure are cumulative. Those with fair complexions living near the equator are most at risk and invariably develop these ‘sun warts’.
Alternating zones of hyper- and parakeratosis overlie a thickened or atrophic epidermis. The normal maturation pattern of the epidermis may be lost and occasional pleomorphic keratinocytes may be seen. Solar elastosis is seen in the superficial dermis.

**Treatment**

Freezing with liquid nitrogen or carbon dioxide snow is simple and effective. Curettage is best for large lesions and cutaneous horns. Multiple lesions, including subclinical ones, can be treated with 5-fluorouracil cream (Formulary 1, p. 338) after specialist advice. The cream is applied once or twice daily until there is a marked inflammatory response in the treated area. This takes about 3 weeks and only then should the applications be stopped. Healing is rapid and most patients are very pleased with their ‘new’ smooth skin. Severe discomfort from the treatment may be alleviated by the short-term application of a local steroid. 5-Fluorouracil cream is more effective for keratoses on the face than on the arms. Alternatively, less effective but causing less inflammation, 5-fluorouracil cream can be applied on just one or two days a week for 8 weeks. Recently, 3% sodium diclofenac made up in a hyaluronan gel has come on the market with a product licence to treat actinic

**Histology**

Alternating zones of hyper- and parakeratosis overlie a thickened or atrophic epidermis. The normal maturation pattern of the epidermis may be lost and occasional pleomorphic keratinocytes may be seen. Solar elastosis is seen in the superficial dermis.
keratoses but it is too early to judge its efficacy. Photodynamic therapy (p. 325), using aminolaevulinic acid hydrochloride followed by blue light, is effective but requires specialist facilities. Lesions that do not respond should be regarded with suspicion, and biopsied.

**Sebaceous naevi (Fig. 18.28)**

A flat hairless area at birth, usually in the scalp, these naevi become yellower and more raised at puberty. Basal cell carcinomas appear on some in adult life.

**Malignant epidermal tumours**

**Basal cell carcinoma (rodent ulcer)**

This is the most common form of skin cancer. It crops up most commonly on the faces of the middle-aged or elderly. Lesions invade locally but, for practical purposes, never metastasize.

**Cause**

Prolonged sun exposure is the main factor so these tumours are most common in white people living near the equator. They may also occur in scars caused by X-rays, vaccination or trauma. Photosensitizing pitch, tar and oils can act as cocarcinogens with ultraviolet radiation. Previous treatment with arsenic, once present in many ‘tonics’, predisposes to multiple basal cell carcinomas, often after a lag of many years.

Multiple basal cell carcinomas are found in the naevoid basal cell carcinoma syndrome (Gorlin’s syndrome) where they may be associated with palmar-plantar pits, jaw cysts and abnormalities of the skull, vertebrae and ribs. The syndrome is inherited as an autosomal dominant trait and recent studies indicate that the genetic abnormality lies on chromosome 9q.

**Presentation**

**Nodulo-ulcerative.** This is the most common type. An early lesion is a small glistening translucent skin-coloured papule that slowly enlarges. Central necrosis, although not invariable, leaves an ulcer with an adherent crust and a rolled pearly edge (Fig. 18.29). Fine telangiectatic vessels often run across the tumour’s surface (Fig. 18.30). Without treatment such lesions may reach 1–2 cm in diameter in 5–10 years.
to be brown or have specks of brown or black within it (Fig. 18.33).

Clinical course

The slow but relentless growth destroys tissue locally. Untreated, a basal cell carcinoma can invade underlying cartilage or bone (Fig. 18.34) or damage important structures such as the tear ducts.

Cystic. The lesion is at first like the nodular type, but later cystic changes predominate and the nodule becomes tense and more translucent, with marked telangiectasia.

Cicatricial (morphoeic). These are slowly expanding yellow or white waxy plaques with an ill-defined edge. Ulceration and crusting, followed by fibrosis, are common, and the lesion may look like an enlarging scar (Fig. 18.31).

Superficial (multicentric). These arise most often on the trunk. Several lesions may be present, each expanding slowly as a pink or brown scaly plaque with a fine ‘whipcord’ edge (Fig. 18.32). Such lesions can grow to more than 10 cm in diameter.

Pigmented. Pigment may be present in all types of basal cell carcinoma causing all or part of the tumour
Histology
Small, darkly blue staining basal cells grow in well-defined aggregates which invade the dermis (Fig. 18.35). The outer layer of cells is arranged in a palisade. Numerous mitoses and apoptotic bodies are seen. In the cicatricial type the islands of tumour are surrounded by fibrous tissue.

Differential diagnosis
A nodular basal cell carcinoma may be confused with an intradermal melanocytic naevus, a squamous cell carcinoma, a giant molluscum contagiosum (p. 209) or a keratoacanthoma. Pigmented basal cell carcinomas should be distinguished from seborrhoeic warts and malignant melanomas. A cicatricial basal cell carcinoma may mimic morphea (p. 129) or a scar. A superficial basal cell carcinoma may be confused with an intraepidermal carcinoma, with psoriasis (Chapter 5) or with nummular eczema (p. 89).

Treatment
There is no single treatment of choice for all basal cell carcinomas. Treatment should be tailored to the type of tumour, its site and the age and general health of the patient. Published guidelines are very useful (see Further reading).

In general, excision, with 0.5 cm of surrounding normal skin, is the treatment of choice for discrete nodular and cystic tumours in patients under 60 years. Cicatricial tumours, with their ill-defined edges, and lesions near vital structures, should be excised by specialist surgeons. Mohs’ micrographic surgical technique is highly effective; it includes careful histological checks in all planes of tissue excised during the operation (see p. 323). Mohs’ surgery is also becoming the treatment of choice for large (> 1 cm) tumours and for those on cosmetically important sites, such as the nose, and for tumours in certain anatomical areas, such as the inner canthus and the nasolabial folds. Radiotherapy is also effective; it is seldom used now for biopsy-proven lesions in patients under 70 years, but is helpful when surgery is contraindicated. Cryotherapy, curettage and cautery and photodynamic therapy are sometimes useful for superficial lesions (p. 325). Sometimes palliative treatment with curettage and cautery may be preferable to aggressive treatment for elderly patients in poor health; nowadays there is seldom justification for doing nothing. The 5-year cure rate for all types of basal cell carcinoma is over 95%, but regular follow-up is necessary to detect local recurrences when they are small and remediable.

Learning Points
1. Catch lesions early: small ones are easy to get rid of; larger ones can eat into cartilage or bone.
2. Do not sit and watch doubtful lesions near the eye.

Squamous cell carcinoma
This is a common tumour in which malignant keratinocytes show a variable capacity to form keratin.
**CHAPTER 18**

**Cells**

Cells usually retain the capacity to produce keratin (Fig. 18.37).

**Treatment**

After the diagnosis has been confirmed by biopsy, the tumour should be excised with a 0.5-cm border of normal skin. Mohs’ micrographic surgery is useful for high-risk tumours. Radiotherapy is effective but should be reserved for the frail and the elderly.

**Malignant melanoma**

Malignant melanoma attracts a disproportionate amount of attention because it is so often lethal. The public now knows more about its increasing incidence and dangers.

**Incidence**

The incidence in white people in the UK and USA is doubling every 10 years. In Scotland and northern parts of the USA the incidence is now about 10 per 100 000 per year, with females being affected more often than males. There is a higher incidence in white people.

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**Cause**

These tumours often arise in skin damaged by long-term ultraviolet radiation and also by X-rays and infrared rays. Other carcinogens include pitch, tar, mineral oils and inorganic arsenic (see Basal cell carcinoma). Certain rare genetic disorders, with defective DNA repair mechanisms, such as xeroderma pigmentosum (p. 304), lead to multiple squamous and basal cell carcinomas, and to malignant melanoma; this illustrates the importance of altered DNA in the pathogenesis of malignancy. The DNA of the human papilloma virus (p. 201) can be integrated into the nuclear DNA of keratinocytes and cause malignant transformation. Immunosuppression and ultraviolet radiation predispose to this.

Multiple self-healing squamous cell carcinomas are found in the autosomal dominant trait described by Ferguson-Smith. The abnormal gene lies on chromosome 9q.

**Clinical presentation and course**

Tumours may arise as thickenings in an actinic keratosis or, de novo, as small scaling nodules; rapidly growing anaplastic lesions may start as ulcers with a granulating base and an indurated edge (Fig. 18.36). Squamous cell carcinomas are common on the lower lip (Fig. 13.36) and in the mouth. Tumours arising in areas of previous X-radiation or thermal injury, chronic draining sinuses, chronic ulcers, chronic inflammation or Bowen’s disease are the most likely to metastasize. Tumours arising in non-exposed sites, such as the perineum and sole of foot and on the ear and lip, have a lesser malignant potential but may metastasize. Squamous cell carcinomas arising in sun-exposed areas and in actinic keratoses seldom metastasize. Tumours more than 2 cm in diameter are twice as likely to recur and metastasize compared with smaller tumours. Metastatic potential is also high in tumours greater than 4 mm in depth or invading to the subcutaneous tissue, in poorly differentiated tumours; in tumours with perineural involvement; and in those arising in the immunosuppressed.

**Histology**

Keratinocytes disrupt the dermo-epidermal junction and proliferate irregularly into the dermis. Malignant cells usually retain the capacity to produce keratin (Fig. 18.37).
people living near the equator than in temperate zones and there the female preponderance is lost. The highest incidence, more than 40 per 100 000 per year, is seen in white people living in Australia and New Zealand. The tumour is rare before puberty and in black people, Asians and Orientals and when it does occur in these races it is most often on the palms, soles or mucous membranes.

Cause

Genetic. Malignant melanomas are most common in white people with blond or red hair, many freckles and a fair skin that tans poorly. Those of Celtic origin are especially susceptible. Ten to 15% of melanomas are familial (occur in families where two or more first-degree relatives have a melanoma). Molecular defects in both tumour suppressor genes and oncogenes have been linked to these melanomas; the one attracting most interest at present lies on chromosome 9p and encodes a tumour suppressor gene designated p16, also known as CDKN2A. Melanoma may affect several members of a single family in association with atypical (dysplastic) naevi (p. 259).

Sunlight. Both the incidence and mortality increase with decreasing latitude. Tumours occur most often, but not exclusively, on exposed skin.

Pre-existing melanocytic naevi. The risk of developing a malignant melanoma is highest in those with atypical naevi, congenital melanocytic naevi or many banal melanocytic naevi. A pre-existing naevus is seen histologically in about 30% of malignant melanomas.

Clinical features

Eighty per cent of invasive melanomas are preceded by a superficial and radial growth phase, shown clinically as the expansion of an irregularly pigmented macule or plaque (Fig. 18.38). Most are multicoloured mixtures of black, brown, blue, tan and pink. Their margins are irregular with reniform projections and notches. Malignant cells are at first usually confined to the epidermis and uppermost dermis, but eventually invade more deeply and may metastasize (Fig. 18.38).

There are four main types of malignant melanoma.

1 Lentigo maligna melanoma occurs on the exposed skin of the elderly. An irregularly pigmented, irregularly shaped macule (a lentigo maligna) may have been enlarging slowly for many years as an in situ melanoma before an invasive nodule (the lentigo maligna melanoma) appears (Fig. 18.39).

2 Superficial spreading melanoma is the most common type in Caucasoids. Its radial growth phase shows varied colours and is often palpable (Figs 18.40 and 18.41). A nodule coming up within such a plaque signifies deep dermal invasion and a poor prognosis (Table 18.4).

3 Acral lentiginous melanoma occurs on the palms and soles and, although rare in Caucasoids, is the most common type in Chinese and Japanese people. The invasive phase is again signalled by a nodule coming up within an irregularly pigmented macule or patch.

4 Nodular melanoma (Fig. 18.42) appears as a pigmented nodule with no preceding in situ phase. It is the most rapidly growing and aggressive type.
Metastatic melanoma has spread to surrounding skin, regional lymph nodes or to other organs. At this stage it can rarely be cured.

**Staging**

The most popular staging systems for melanoma are the TNM classification (Europe) and the American Melanomas can also described by their colour, site and degree of spread.

- **Totally amelanotic melanomas** (Fig. 18.43) are rare and occur especially on the soles of the feet. Flecks of pigment can usually be seen with a lens.
- **Subungual melanomas** are painless areas of pigmentation expanding under the nail and onto the nail fold.

**Fig. 18.38** Radial intraepidermal growth phase of melanoma (1 and 2) precedes vertical and invasive dermal growth phase (3).

**Fig. 18.39** This elderly patient, her friends and family doctor, had ignored for too long the slowly spreading macule of a lentigo maligna: now she has a frankly invasive melanoma within it (the darker area).

**Fig. 18.40** Superficial spreading melanoma of the jawline. Small, and still curable at this stage.

- **Metastatic melanoma** has spread to surrounding skin, regional lymph nodes or to other organs. At this stage it can rarely be cured.
Joint Committee on Cancer (AJCC) system in the USA (Table 18.4). They provide a useful guide to prognosis (see also Table 18.5).

**Histology**

- **Lentigo maligna.** Numerous atypical melanocytes, many in groups, are seen along the basal layer extending downwards in the walls of hair follicles.
- **Lentigo maligna melanoma.** Dermal invasion occurs, with a breach of the basement membrane region. *In situ* changes are seen in the adjacent epidermis.
- **Superficial spreading melanoma in situ.** Large epithelioid melanoma cells permeate the epidermis. **Superficial spreading melanoma.** The dermal nodule may be composed of epithelioid cells, spindle cells or naevus-like cells. *In situ* changes are seen in the adjacent epidermis.
• **Acral lentiginous melanoma** in situ. Atypical melanocytes are seen in the base of the epidermis and permeating the mid epidermis.
• **Acral lentiginous melanoma**. Melanoma cells invade the dermis. *In situ* changes are seen in the adjacent epidermis.
• **Nodular melanoma**. The tumour comprises epithelioid, spindle and naevoid cells and there is no *in situ* melanoma in the adjacent epidermis.

### Microstaging

The histology (Fig. 18.44) can be used to assess prognosis. Breslow’s method is to measure, with an ocular micrometer, the vertical distance from the granular cell layer to the deepest part of the tumour. Clark’s method is to assess the depth of penetration of the melanoma (Fig. 18.45) in relation to the different

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth of primary tumour</strong></td>
<td>Breslow</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.75 mm, 5-year survival 95%</td>
</tr>
<tr>
<td></td>
<td>0.76–1.5 mm, 5-year survival 85%</td>
</tr>
<tr>
<td></td>
<td>1.51–4.0 mm, 5-year survival 65%</td>
</tr>
<tr>
<td></td>
<td>&gt; 4.0 mm, 5-year survival 45%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Females do better than males</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Prognosis worsens after 50 years of age, especially in males</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>The prognosis is poor for tumours on trunk, upper arms, neck and scalp</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td>Signifies a poor prognosis</td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
<td>Prognosis worsens with advancing stage (see Table 18.4)</td>
</tr>
</tbody>
</table>

### Table 18.5 Prognostic indicators in malignant melanoma.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td><strong>Depth of primary tumour</strong></td>
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</tr>
</tbody>
</table>

**Fig. 18.44** Histology of the different types of melanoma.
SKIN TUMOURS

layers of the dermis. The thicker and more penetrating a lesion, the worse is its prognosis (see below).

Differential diagnosis

This includes a melanocytic naevus, seborrhoeic keratosis, pigmented actinic keratosis, pigmented basal cell carcinoma and sclerosing haemangioma; all are discussed in this chapter. A malignant melanoma can also be confused with a subungual or peri-ungual haematoma (see Fig. 13.21). A history of trauma helps here, as may paring. ‘Talon noir’ (Fig. 18.46) is a pigmented petechial area on the heel following minor trauma from ill-fitting training shoes. An amelanotic melanoma is most often confused with a pyogenic granuloma and with a squamous cell carcinoma.

Prognosis

The prognostic indicators, and their significance, are listed in Table 18.5. They have been established by following up large numbers of patients who have undergone appropriate surgical treatment (see below).

Treatment

Surgery. Surgical excision, with minimal delay, is required. An excision biopsy, with a 2-mm margin of clearance laterally, and down to the subcutaneous fat, is recommended for all suspicious lesions. If the histology confirms the diagnosis of malignant melanoma then wider excision, including the wound of the excision biopsy, should be performed as soon as possible. A minimum of 0.5 cm clearance for in situ melanomas and 1 cm clearance is required for all invasive melanomas. Nowadays many surgeons excise 1 cm of normal skin around the tumour (or wound) for every millimetre of tumour thickness, up to 3 mm (Fig. 18.47). The maximum clearance is thus 3 cm of normal skin and, depending on the site, primary closure—without grafting—is often possible. There is
CHAPTER 18

as the disease advances. Many ongoing trials are investigating the role of immunotherapy (e.g. with melanoma-specific antigens) as an adjunct to surgery in patients with poor prognostic (e.g. TNM stages II and III) melanomas. Low dose $\alpha$-interferon appears to improve the disease-free survival time and high-dose regimens may improve overall survival rates. The results of randomized control studies of adjunctive treatment with various melanoma vaccines are awaited with interest.

**Chemotherapy.** Although rarely curative, chemotherapy may be palliative in 25% of patients with stage III melanoma.

**Paget’s disease of the nipple** (Fig. 18.48)

A well-defined red scaly plaque spreads slowly over and around the nipple. It is caused by the invasion of the epidermis by cells from an underlying intraductal carcinoma of the breast (Paget cells). The condition is unilateral, whereas eczema usually affects both nipples. A skin biopsy should be carried out first and if the diagnosis is confirmed mastectomy will be

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**LEARNING POINTS**

1. Prevention of a malignant melanoma is better than cure. Remember avoidance of excessive sun exposure and ‘sun smart’ advice to patients.
2. Everyone, and especially those with many moles, should be encouraged to examine their own skin regularly.
3. Take any change in a mole seriously.
4. Do not forget the ABCDE rules when querying a melanoma (Table 18.3).
5. Excise all doubtful lesions and check their histology.
6. If excision biopsy shows that an invasive melanoma is less than 1 mm thick, the only question to be asked is whether it has been excised with a 1-cm clearance in all directions.
7. Support campaigns to educate doctors and the public to recognize melanoma early, in its superficial and curable phase.

---

Fig. 18.47 Such a wide excision and unsightly graft is no longer acceptable for a thin good-prognosis melanoma. Note the many atypical moles.
SKIN TUMOURS

‘Port-wine’ stains

These are also present at birth and are caused by dilated dermal capillaries. They are pale, pink to purple macules, and vary from the barely noticeable to the grossly disfiguring. Most occur on the face or trunk. They persist, and in middle age may darken and become studded with angiomatous nodules (Fig. 18.49). Occasionally a port-wine stain of the trigeminal area (Fig. 18.50) is associated with a vascular malformation of the leptomeninges on the same side, which may cause epilepsy or hemiparesis (the Sturge–Weber syndrome), or with glaucoma.

Excellent results have been obtained with careful—and time-consuming—treatment with a 585-nm flashlamp-pumped pulsed dye laser (p. 327). Treatment sessions can begin in babies and anaesthesia is not always necessary. If a trial patch is satisfactory, 40–50 pulses can be delivered in a session and the procedure can be repeated at 3-monthly intervals. On the other hand, some adults become very adept at using cosmetic camouflage (see Fig. 1.6).

Combined vascular malformations of the limbs

A large port-wine stain of a limb may be associated with overgrowth of all the soft tissues of that limb with or without bony hypertrophy. There may be underlying venous malformations (Klippel–Trenaunay syndrome), arteriovenous fistulae (Parkes Weber syndrome) or mixed venous–lymphatic malformations.

Table 18.6 Common vascular naevi.

<table>
<thead>
<tr>
<th>Malformations</th>
<th>Present at birth. Do not involute (‘salmon’ patch is exception)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Capillary</td>
<td>(‘salmon’ patch and ‘port-wine’ stain)</td>
</tr>
<tr>
<td>2 Arterial</td>
<td></td>
</tr>
<tr>
<td>3 Venous</td>
<td></td>
</tr>
<tr>
<td>4 Combined</td>
<td></td>
</tr>
</tbody>
</table>

Haemangiomas (sometimes called angiomatous naevi)

Usually appear after birth. More common in females, 50–60% on head and neck. Involute by 5–9 years after initial proliferation

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>1 Superficial</td>
<td>(capillary)</td>
</tr>
<tr>
<td>2 Deep</td>
<td>(cavernous)</td>
</tr>
<tr>
<td>3 Mixed</td>
<td></td>
</tr>
</tbody>
</table>

Essential. Extramammary Paget’s disease affects sites bearing apocrine glands (p. 161) and is caused by an underlying ductal carcinoma of these.

Tumours of the dermis

Benign

Developmental abnormalities of blood vessels

These are either present at birth or appear soon after. They can be classified clinically (Table 18.6) but there is no good clinicohistological correlation. A capillary malformation is composed of a network of capillaries in the upper and mid dermis. A capillary cavernous haemangioma has multiple ectatic channels of varying calibre distributed throughout the dermis and even the subcutaneous fat.

Malformations

‘Salmon’ patches (‘stork bites’)

These common malformations, present in about 50% of all babies, are caused by dilated capillaries in the superficial dermis. They are dull red, often telangiectatic macules, most commonly on the nape of the neck (‘erythema nuchae’), the forehead and the upper eyelids. Nuchal lesions may remain unchanged, but patches in other areas usually disappear within a year.
Capillary cavernous haemangioma
(strawberry naevus)

Strawberry naevi appear within a few weeks of birth, and grow for a few months, forming a raised compressible swelling with a bright red surface (Fig. 18.51). Spontaneous regression then follows; the surface whitens centrally (Fig. 18.52) and regression is complete by the age of 5 years in 50% of children and in 90% by the age of 9, leaving only an area of slight atrophy. Bleeding may follow trauma, and ulceration is common in the napkin (diaper) area.

Observation and encouragement is the management of choice for the great majority. Serial photographs of the way they clear up in other children help parents to accept this. Firm pressure may be needed to stop bleeding. If lesions interfere with feeding, or with vision, or if giant lesions sequestrate platelets (the Kasabach–Merritt syndrome), high doses of systemic steroids should be considered; they are most successful in the proliferative phase. Prednisolone (2–4 mg/kg/day) is given as a single dose in the morning and the dosage tapered to zero after 1 month. Ophthalmological help should be sought for all growing periocular haemangiomas; intralesional steroids have proved effective. Sometimes pulsed tuneable dye lasers are used for treating large lesions in infancy. Rarely, plastic surgery is necessary for a few large and unsightly haemangiomas that fail to improve spontaneously or to regress with the above measures.
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The histology should always be checked. A pyogenic granuloma shows leashes of vessels of varying calibre covered by a thin, often ulcerated, epidermis.

Lesions should be removed by curettage under local anaesthetic with cautery to the base. Rarely, this is followed by recurrence or an eruption of satellite lesions around the original site.

Other benign dermal tumours

Dermatofibromas (histiocytomas)

These benign tumours are firm discrete usually solitary dermal nodules (Fig. 18.55), often on the extrem-
leiomyoma, angiolipoma, neurofibroma (rarely) and dermatofibroma (rarely)).

Keloid

This is an overgrowth of dense fibrous tissue in the skin, arising in response to trauma, however trivial. The tendency to develop keloids is genetically inherited. Keloids are common in Negroids and may be familial. Keloid formation is encouraged by infection, foreign material and by wounds (including surgical ones) especially those not lying along the lines of least tension or the skin creases. Even in Caucasoids, keloids are seen often enough on the presternal area, the neck, upper back and deltoid region of young adults to make doctors think twice before removing benign lesions there. Silicone sheeting and intraleisional steroid injections are helpful but treatment should be given early, preferably for developing lesions.

Lipomas

Lipomas are common benign tumours of mature fat cells in the subcutaneous tissue. There may be one or many (Fig. 18.56) and lipomas are rarely a familial trait. They are most common on the proximal parts of the limbs but can occur at any site. They have an irregular lobular shape and a characteristic soft rubbery consistency. They are rarely painful. They need to be removed only if there is doubt about the diagnosis or if they are painful or unsightly.
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in up to 20% of cases but systemic features such as headaches, flushing and palpitations are unusual.

Malignant

Kaposi’s sarcoma

This malignant tumour of proliferating capillaries and lymphatics may be multifocal. There are two types: the classical, and that associated with immunosuppression. Human herpesvirus type 8 (HHV8) has been isolated from, and linked to, both types.

Classical Kaposi’s sarcoma is seen most often in Africans and in elderly Jews of European origin. The tumours are usually on the feet and ankles but may be seen on the hands and on cold parts of the skin (e.g. the ears and nose). Initially they are dark blue to purple macules progressing to tumours and plaques which ulcerate and fungate. The rate of spread is variable but often slow. Tumours may metastasize to lymph nodes and spread to internal organs; oedema of the legs may be severe.

These tumours are very sensitive to radiotherapy which is the treatment of choice during the early stages; chemotherapy, with chlorambucil or vinblastine, helps when there is systemic involvement. Life expectancy is 5–9 years.

Kaposi’s sarcoma and immunosuppression (see Figs 14.32–14.34). Smaller and more subtle (e.g. bruise-like) lesions may occur in an immunodeficient host. This tumour has recently become well known because of its association with AIDS (p. 211) caused by the human immunodeficiency virus (HIV-1). Lesions of AIDS-related Kaposi’s sarcoma can appear anywhere but are most common on the upper trunk and head and neck. The initial bruise-like lesions tend to follow tension lines; they become raised, increasingly pigmented and evolve into nodules and plaques. Lesions frequently arise on the oral mucous membranes. Interestingly, HIV-positive intravenous drug abusers do not develop Kaposi’s sarcoma as often as do HIV-positive homosexuals. The prognosis of AIDS patients with Kaposi’s sarcoma is poor as most will develop opportunistic infections and the life expectancy in this situation is around 1 year. Single lesions respond to radiotherapy, cryotherapy or intralesional vinblastine; systemic treatment with α-interferon has helped some with multiple lesions.
Lymphomas and leukaemias

Skin involvement falls into two broad categories:

1. Disorders which arise in the skin or preferentially involve it. These include:
   - T-cell lymphoma (mycosis fungoides);
   - Sézary syndrome; and
   - lymphoma associated with HIV infection.

2. Those arising extracutaneously, but which sometimes involve the skin. These include:
   - Hodgkin’s disease;
   - B-cell lymphoma; and
   - leukaemia.

Cutaneous T-cell lymphoma (CTCL; sometimes called mycosis fungoides)

This lymphoma of skin-associated helper T lymphocytes usually evolves slowly. There are three clinical phases: the patch, plaque and tumour stages, with involvement of lymph nodes and other tissues occurring late in the disease.

The **patch stage** (formerly termed ‘premycotic’ to denote an early phase of mycosis fungoides) may last for years (see Fig. 6.9). Most commonly it consists of scattered, barely palpable, erythematous, slightly pigmented, sharply marginated scaly patches rather like psoriasis or seborrhoeic dermatitis. Often they have a bizarre outline (e.g. arciform, or horseshoe-shaped) and, on close inspection, atrophy with surface wrinkling is usually evident. Their distribution is usually asymmetrical. Less commonly, the patch stage can be a widespread poikilodermat, with atrophy, pigmentation and telangiectasia (Fig. 18.58). As the lymphoma develops, some patches become indurated and palpable: the **plaque stage**. Some then turn into frank tumours which may become large (occasionally like mushrooms, hence the term ‘mycosis fungoides’) and ulcerate (Fig. 18.59). The patch stage of CTCL may be difficult to diagnose clinically, but the plaque and tumour stages are usually characteristic. The first two phases of the disease may occupy 20 years or more, but the tumour stage is often short, with spread and death usually within 3 years.

The Sézary syndrome is also a CTCL caused by a proliferation of helper T lymphocytes. Generalized skin erythema and oedema is associated with pruritus...
and lymphadenopathy. Abnormal T lymphocytes, with large convoluted nuclei, are found circulating in the blood (‘Sézary cells’).

**Histology**

The histological hallmarks of plaque stage CTCL are:

- intraepidermal lymphocytic microabscesses (Pautrier microabscesses);
- a band of lymphoid cells in the upper dermis, infiltrating the epidermis; and
- atypical lymphocytes.

The histology of the patch stage poses more problems and may differ little from dermatitis. Immunophenotyping and T-cell receptor gene rearrangement studies (p. 19) are not always helpful in reaching a definitive diagnosis. Many biopsies, over several years, may be needed to prove that a suspicious rash is indeed an early stage of CTCL.

**Differential diagnosis**

The patch and plaque stages may be mistaken for psoriasis or parapsoriasis (Chapter 5), seborrhoeic dermatitis (p. 87) or tinea corporis (p. 216). However, they respond poorly to treatment for these disorders; the bizarre shapes of the patches and their asymmetrical distribution often raise suspicion. In the early stages skin scrapings may be needed to exclude tinea.

**Treatment**

Moderately potent or potent local steroids, and UVB treatment, may provide prolonged palliation in the patch stage. In the plaque stage, PUVA, oral retinoids and α-interferon are helpful. If lesions become more indurated, electron beam therapy may be used. Topical nitrogen mustard paint has also been used with success in both patch and plaque stages. Individual tumours respond well to low-dose radiotherapy. Systemic chemotherapy is disappointing.

**Extracutaneous lymphomas**

**Hodgkin’s disease**

This is of interest to dermatologists because it may present with severe generalized pruritus (p. 291).

Patients with unexplained pruritus must be examined for lymphadenopathy and hepatosplenomegaly. Only rarely does Hodgkin’s disease affect the skin directly, as small nodules and ulcers.

**Leukaemia**

Rarely, the first sign of leukaemia is a leukaemic infiltrate in the skin. Clinically, this shows as plum-coloured plaques or nodules or, less often, a thickening and rugosity of the scalp (cutis verticis gyratum). More often, the rashes associated with leukaemia are non-specific red papules (‘leukaemids’). Other non-specific manifestations include pruritus, herpes zoster, acquired ichthyosis and purpura.

**B-cell lymphomas**

B-lymphocytic lymphomas presenting with skin lesions are rare. They appear as scattered plum-coloured nodules (Fig. 18.60). Histologically, a B-cell lymphoma infiltrates the lower dermis in a nodular or diffuse manner. Immunophenotyping shows a monoclonal
expansion of B lymphocytes. Treatment is with radiotherapy and systemic chemotherapy.

Other malignant tumours

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans is a slowly growing malignant tumour of fibroblasts, arising usually on the upper trunk. At first it seems like a dermatofibroma or keloid but, as it slowly expands, it turns into a plaque of red or bluish nodules with an irregular protuberant surface. It seldom metastasizes. It should be removed with extra wide margins, and even then will sometimes recur.

Cutaneous metastases

About 3% of patients with internal cancers have cutaneous metastases. They usually arise late and indicate a grave prognosis, but occasionally a solitary cutaneous metastasis is the first sign of the occurrence of a tumour.

The most common cutaneous metastases come from breast cancer. The skin of the breast is also most often involved by the direct extension of a tumour. This may show up as a sharply demarcated and firm area of erythema (carcinoma erysipeloides), firm telangiectatic plaques and papules (carcinoma telangiectoides) or as skin like orange peel (peau d’orange) caused by blocked and dilatated lymphatics. Carcinoma of the breast may also send metastases to the scalp causing patches of alopecia (Fig. 18.61), or to other areas as firm and discrete dermal nodules.

Other common primaries metastasizing to the skin are tumours of the lung, gastrointestinal tract, uterus, prostate and kidney. The most frequent sites for secondary deposits are the umbilicus and the scalp.

Further reading

Only selected aspects of this huge subject can be covered here. In the first part of this chapter, the skin changes seen in particular diseases (e.g. sarcoidosis) or groups of diseases (e.g. internal malignancies) are described. The second part covers some individual skin conditions that can be associated with a wide range of internal disorders (e.g. pyoderma gangrenosum). Finally, although pregnancy is not a disease, for convenience its skin manifestations are listed here too.

**The skin and internal malignancy**

Obvious skin signs can be seen if a tumour invades the skin, or sends metastases to it; but there are other more subtle ways in which tumours can affect the skin. Sometimes they act physiologically, causing, for example, the acne seen with some adrenal tumours, flushing in the carcinoid syndrome, and jaundice with a bile duct carcinoma. These cast-iron associations need no further discussion here. However, the presence of some rare but important conditions should alert the clinician to the possibility of an underlying neoplasm.

1. **Acanthosis nigricans** is a velvety thickening and pigmentation of the major flexures. Setting aside those cases caused by obesity (Fig. 19.1), by diabetes and characterized by insulin resistance, or by drugs such as nicotinic acid used to treat hyperlipidaemia, the chances are high that a tumour is present, usually within the abdominal cavity.

2. **Erythema gyratum repens** is a shifting pattern of waves of erythema covering the skin surface and looking like the grain on wood.

3. **Acquired hypertrichosis lanuginosa** (‘malignant down’) is an excessive and widespread growth of fine lanugo hair.

4. **Necrolytic migratory erythema** is a figurate erythema with a moving crusted edge. When present, usually with anaemia, stomatitis, weight loss and diabetes, it signals the presence of a glucagon-secreting tumour of the pancreas.

5. **Bazex syndrome** is a papulosquamous eruption of the fingers and toes, ears and nose, seen with some tumours of the upper respiratory tract.

6. **Dermatomyositis**, other than in childhood (p. 125).

7. **Generalized pruritus**. One of its many causes is an internal malignancy, usually a lymphoma (p. 291).

8. **Superficial thrombophlebitis**. The migratory type has traditionally been associated with carcinomas of the pancreas.

9. **Acquired ichthyosis**. This may result from a number of underlying diseases (see p. 43) but it is always important to exclude malignancy, especially lymphomas, as the cause.

Fig. 19.1 Acanthosis nigricans—in this case caused by obesity.
will have diabetes. The remaining few should have a glucose tolerance test followed by regular urine tests as some will become diabetic later. The lesions appear as one or more discoloured areas on the fronts of the shins (Fig. 19.3); they are shiny, atrophic and brown-red or slightly yellow. The underlying blood vessels are easily seen through the atrophic skin and the margin may be erythematous or violet. Minor knocks can lead to slow-healing ulcers; biopsy can do the same. No treatment is reliably helpful.

2 Granuloma annulare. The cause of granuloma annulare is not known and dermatologists still debate whether or not there is a genuine association with diabetes. If it exists at all, the association applies only to a few adults with extensive lesions. Children with standard lesions on the hands may need a single urine check for sugar but no more elaborate tests. Clinically, the lesions of granuloma annulare often lie over the knuckles and are composed of dermal nodules fused into a rough ring shape (Fig. 19.4). On the hands the lesions are skin-coloured or slightly pink; elsewhere a purple colour may be seen. Although a biopsy is seldom necessary, the histology shows a diagnostic palisading granuloma, like that of necrobiosis lipoidica. Lesions tend to go away over the

10 Genetic conditions. One example is the Muir–Torre syndrome in which sebaceous adenomas are accompanied by surprisingly unaggressive visceral malignancies.

11 Acute febrile neutrophilic dermatosis (Sweet’s syndrome; Fig. 19.2). The classic triad found in association with the red oedematous plaques consists of fever, a raised erythrocyte sedimentation rate (ESR) and a raised blood neutrophil count. The most important internal association is with myeloproliferative disorders.

12 Others. Pachydermoperiostosis is a coarsening and thickening of the skin seen in association with severe clubbing. It can be inherited as an autosomal dominant trait, or be a result of the standard causes of clubbing which include conditions such as bronchial carcinoma.

The skin and diabetes mellitus

The following are more common in those with diabetes than in others.

1 Necrobiosis lipoidica. Less than 1% of diabetics have necrobiosis, but most patients with necrobiosis

Fig. 19.2 Acute febrile neutrophilic dermatosis (Sweet’s syndrome).

Fig. 19.3 Necrobiosis lipoidica: shiny yellowish patch with marked telangiectasia.
The skin in sarcoidosis

About one-third of patients with systemic sarcoidosis have skin lesions; it is also possible to have cutaneous sarcoidosis without systemic abnormalities. The most important skin changes are as follows.

1. **Erythema nodosum** (see Fig. 8.10). This occurs in the early stages of sarcoidosis, especially in young women.
2. **Scar sarcoidosis**. Granulomatous lesions arising in longstanding scars should raise suspicions of sarcoidosis.
3. **Lupus pernio**. Dusky infiltrated plaques appear on the nose and fingers, often in association with sarcoidosis of the upper respiratory tract.
4. **Papular, nodular and plaque forms** (Fig. 19.6). These brownish-red, violaceous, or hypopigmented papules and plaques are indolent although often symptom-free. Sometimes they are annular. They vary in number, size and distribution. Intralesional and topical corticosteroids are sometimes helpful and hydroxychloroquine (Formulary 2, p. 351) has been used successfully. Chronic lesions respond poorly to any line of treatment short of systemic steroids, which are usually best avoided if involvement is confined to the skin.

The skin in liver disease

Some of the associated abnormalities are the following.

1. **Pruritus**. This is related to obstructive jaundice and may precede it (p. 291).

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Fig. 19.4 Granuloma annulare.

Fig. 19.5 Diabetic cheiropathy—the prayer sign. Poor finger apposition in the diabetic hand (on the left) compared with the normal one (on the right).
3 **Half-and-half nail.** The proximal half is white and the distal half is pink or brownish.

4 *Perforating disorders*. Small papules in which collagen or elastic fibres are being extruded through the epidermis.

5 *Pseudoporphyria* (p. 289).

6 The skin changes of the conditions leading to renal disease. For example, leucocytoclastic vasculitis (p. 102), connective tissue disorders (Chapter 10), Fabry’s disease (p. 291).

**Graft-vs.-host disease**

Marrow grafting is now used for several disorders including aplastic anaemia and leukaemia. Immuno-logically competent donor lymphocytes, however, may cause problems by reacting against host tissues, especially the skin, liver and gut.

Acute graft-vs.-host (GVH) disease appears within 4 weeks. Fever accompanies malaise and a worsening morbilliform rash, which may progress to a generalized desquamation or even toxic epidermal necrolysis. Chronic GVH disease occurs later: its skin changes are variable but may be like those of lichen planus or a pigmented scleroderma. The skin changes may be severe enough to need treatment with systemic prednisolone and azathioprine, PUVA or cyclosporin A.

**Malabsorption and malnutrition**

Some of the most common skin changes are listed in Table 19.1.

**The porphyrias**

There are at least seven enzymes in the metabolic pathway that leads to the synthesis of haem. There are also seven different types of porphyria, each being caused by a deficiency of one of these enzymes, and each having its own characteristic pattern of accumulation of porphyrin and porphyrin precursors. Some of these cause the photosensitivity (to ultraviolet radiation of wavelength 400 nm, which is capable of penetrating through window glass) that is the cardinal feature of the cutaneous porphyrias.

The different types can be separated on clinical grounds, aided by the biochemical investigation of
Erythrohepatic protoporphyria (erythropoietic protoporphyria)

In this more common, autosomal dominant condition, caused by mutations in the ferrochelatase gene, a less severe photosensitivity develops during childhood. A burning sensation occurs within minutes of exposure to sunlight. Soon the skin becomes swollen and crusted vesicles sometimes appear, leading to pitted scars. Liver disease and gallstones occur. In addition to sun avoidance and the use of sunscreens (Formulary 1, p. 330), beta-carotene may be given orally.

Cutaneous hepatic porphyria (porphyria cutanea tarda)

There are two types: a sporadic type (accounting for 80% of cases) and a type inherited as an autosomal...
Acute intermittent porphyria

This condition, inherited as an autosomal dominant trait as a result of mutations of the porphobilinogen deaminase gene, is most common in Scandinavia. Skin lesions do not occur. Attacks of abdominal pain, accompanied by neuropsychiatric symptoms and the passage of dark urine, are sometimes triggered by drugs (especially barbiturates, griseofulvin, oestrogens and sulphonamides).

Variegate porphyria

This disorder, inherited as an autosomal dominant trait, and a result of mutations of the protoporphyrinogen oxidase gene, is particularly common in South Africa. It shares the skin features of porphyria
cutanea tarda and the systemic symptoms and drug provocation of acute intermittent porphyria.

‘Pseudoporphyrria’
This term is used when skin changes like those of cutaneous hepatic porphyria occur without an underlying abnormality of porphyrin metabolism. It is seen in a few patients on haemodialysis, and can be induced by some drugs—notably frusemide (furosemide) and non steroidal anti-inflammatory drugs. The overuse of sun beds is another possible cause.

Some metabolic disorders

Amyloidosis
Amyloid is a protein that can be derived from several sources, including immunoglobulin light chains and probably keratins. It is deposited in the tissues under a variety of circumstances and is then usually in combination with a P component derived from the plasma. Systemic amyloidosis of the type that is secondary to chronic inflammatory disease, such as rheumatoid arthritis or tuberculosis, tends not to affect the skin. In contrast, skin changes are prominent in primary systemic amyloidosis, and also in the amyloid associated with multiple myeloma. Skin blood vessels infiltrated with amyloid rupture easily, causing ‘pinch purpura’ to occur after minor trauma. The waxy deposits of amyloid, often most obvious around the eyes, may also be purpuric. Distinct from the systemic amyloidoses are localized deposits of amyloid. These are uncommon and usually take the form of macular areas of rippled pigmentation, or of plaques made up of coalescing papules. Both types are itchy.

Mucinoses
The dermis becomes infiltrated with mucin in certain disorders.
1 Myxoedema. In the puffy hands and face of patients with hypothyroidism.
2 Pretibial myxoedema. Pink or flesh-coloured mucinous plaques are seen on the lower shins, together with marked exophthalmos, in some patients with hyperthyroidism. They may also occur after the thyroid abnormality has been treated.
3 Scleromyxoedema. A diffuse thickening and papulation of the skin may occur in connection with an immunoglobulin G (IgG) monoclonal paraproteinaemia.
4 Follicular mucinosis. In this condition, the infiltrated plaques show a loss of hair. Some cases are associated with a lymphoma.

Xanthomas
Deposits of fatty material in the skin and subcutaneous tissues (xanthomas) may provide the first clue to important disorders of lipid metabolism.
Primary hyperlipidaemias are usually genetic. They fall into six groups, classified on the basis of an analysis of fasting blood lipids and electrophoresis of plasma lipoproteins. All, save type I, carry an increased risk of atherosclerosis—in this lies their importance and the need for treatment.
Secondary hyperlipidaemia may be found in a variety of diseases including diabetes, primary biliary cirrhosis, the nephrotic syndrome and hypothyroidism.
The clinical patterns of xanthoma correlate well with the underlying cause. The main patterns and their most common associations are shown in Table 19.2.

Phenylketonuria
Phenylketonuria is a rare metabolic cause of hypopigmentation. Its prevalence is about 1 in 25 000. It is inherited as an autosomal recessive trait, the abnormal gene lying on chromosome region 12q22-q24, and is caused by a deficiency of the liver enzyme phenylalanine hydroxylase, which catalyses the hydroxylation
of phenylalanine to tyrosine. This leads to the accumulation of phenylalanine, phenylpyruvic acid and their metabolites.

Affected individuals have fair skin and hair. They often develop eczema, usually of atopic type, and may be photosensitive. The accumulation of phenylalanine and its metabolites damages the brain during the phase of rapid development just before and just after birth. Mental retardation, epilepsy and extrapyramidal manifestations such as athetosis and mental retardation may then occur.

Table 19.2 Xanthomas: clinical appearance and associations.

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical appearance</th>
<th>Types of hyperlipidaemia (Frederickson classification) and associated metabolic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthelasma palpebrarum (Fig. 19.11)</td>
<td>Soft yellowish plaques on the eyelids</td>
<td>None or type II, III or IV</td>
</tr>
<tr>
<td>Tuberous xanthomas (Fig. 19.12)</td>
<td>Firm yellow papules and nodules, most often on points of knees and elbows</td>
<td>Types II, III and secondary</td>
</tr>
<tr>
<td>Tendinous xanthomas</td>
<td>Subcutaneous swellings on fingers or by Achilles tendon</td>
<td>Types II, III and secondary</td>
</tr>
<tr>
<td>Eruptive xanthomas</td>
<td>Sudden onset, multiple small yellow papules</td>
<td>Types I, IV, V and secondary (usually to diabetes)</td>
</tr>
<tr>
<td>Plane xanthomas (Fig. 19.13)</td>
<td>Yellow macular areas at any site</td>
<td>Type III and secondary</td>
</tr>
<tr>
<td>Plane xanthomas (Fig. 19.13)</td>
<td>Yellow palmar creases</td>
<td>Type III and secondary</td>
</tr>
<tr>
<td>Generalized plane xanthomas</td>
<td>Yellow macules lesions over wide areas</td>
<td>Myeloma</td>
</tr>
</tbody>
</table>

Fig. 19.12 Tuberous xanthoma on the points of the elbows—a mixture of nodules and papules.

Fig. 19.13 Plane xanthoma with yellow palmar creases.
Oculocutaneous albinism can usually be distinguished by its eye signs. The Guthrie test, which detects raised blood phenylalanine levels, is carried out routinely at birth in most developed countries.

A low-phenylalanine diet should be started as soon as possible to prevent further neurological damage.

Alkaptonuria

In this rare recessively inherited disorder, based on a homogentisic acid oxidase deficiency, dark urine may be seen in childhood, and in adult life pigment may be deposited in various places including the ears and sclera. Arthropathy may occur.

Fabry’s disease (angiokeratoma corporis diffusum)

A deficiency of the enzyme α-galactosidase A is found in this sex-linked disorder (chromosome region Xq21.3–22); abnormal amounts of glycolipid are deposited in many tissues as a result. The skin lesions are grouped, almost black, small telangiectatic papules especially around the umbilicus and pelvis. Progressive renal failure occurs in adult life. Most patients have attacks of excruciating unexplained pain in their hands. Some female carriers have skin changes, although these are usually less obvious than those of affected males. Similar skin lesions may be seen in lysosomal storage disorders such as fucosidosis.

Generalized pruritus

Pruritus is a symptom with many causes, but not a disease in its own right. Itchy patients fall into two groups: those whose pruritus is caused simply by surface causes (e.g. eczema, lichen planus and scabies), which seldom need much investigation; and the others, who may or may not have an internal cause for their itching, such as the following.

1 Liver disease. Itching signals biliary obstruction. It is an early symptom of primary biliary cirrhosis. Cholestyramine often helps cholestatic pruritus, possibly by promoting the elimination of bile salts.

2 Chronic renal failure. Urea itself seems not to be responsible for this symptom, which plagues about one-third of patients undergoing renal dialysis.

3 Iron deficiency. Treatment with iron may help the itching.

4 Polycythaemia. The itching here is usually triggered by a hot bath; it has a curious pricking quality and lasts about an hour.

5 Thyroid disease. Itching and urticaria may occur in hyperthyroidism. The dry skin of hypothyroidism may also be itchy.

6 Diabetes. Generalized itching may be a rare presentation of diabetes.

7 Internal malignancy. The prevalence of itching in Hodgkin’s disease may be as high as 30%. It may be unbearable, yet the skin often looks normal. Pruritus may occur long before other manifestations of the disease. Itching is uncommon in carcinomatosis.

8 Neurological disease. Paroxysmal pruritus has been recorded in multiple sclerosis and in neurofibromatosis. Brain tumours infiltrating the floor of the fourth ventricle may cause a fierce persistent itching of the nostrils.

9 The skin of the elderly may itch because it is too dry.

The search for a cause has to be tailored to the individual patient, and must start with a thorough history and physical examination. The presence of a ‘butterfly sign’ (Fig. 19.14) sometimes suggests an internal cause for the itching. Unless a treatable cause is found, therapy is symptomatic and consists of sedative antihistamines, and the avoidance of rough clothing, overheating and vasodilatation, including that brought on by alcohol. UVB may help the itching associated with chronic renal, and perhaps liver disease. Local

Fig. 19.14 An example of the butterfly sign. This lady could not reach her upper back but could scratch her skin everywhere else. In other patients, the spared area is shaped more like a butterfly.
**LEARNING POINTS**

1. Learn how to spell pruritus (not pruritis) but do not accept it as a diagnosis in its own right.
2. Ponder underlying causes in those with no primary skin disease.

Applications include calamine and mixtures containing small amounts of menthol or phenol (Formulary 1, p. 330). Sometimes lubricating the skin with emollients helps.

**Pyoderma gangrenosum**

An inflamed nodule or pustule breaks down centrally to form an expanding ulcer with a polycyclic or serpiginous outline, and a characteristic undermined bluish edge (Fig. 19.15). The condition is not bacterial in origin but its pathogenesis, presumably immunological, is not fully understood. It may arise in the absence of any underlying disease, but tends to associate with the following conditions.

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**Fig. 19.15** Pyoderma gangrenosum: a plum-coloured lesion with a typical cribriform appearance.

**Fig. 19.16** This longstanding ulcer was pyoderma gangrenosum secondary to the patient’s rheumatoid arthritis. (Courtesy of Dr G.W. Beveridge, The Royal Infirmary of Edinburgh, Edinburgh, UK.)

**Fig. 19.17** Another manifestation of Crohn’s disease: grossly oedematous vulva with interconnecting sinuses. Biopsy at the site arrowed showed a granulomatous histology.

1. Ulcerative colitis.
2. Conditions causing polyarthritis, including rheumatoid arthritis (Fig. 19.16).
3. Crohn’s disease (Fig. 19.17).
5. Leukaemia (with a bullous form of pyoderma).
Lesions may be single or multiple. If gut disease is present then control of this will help the pyoderma. Otherwise the condition responds to systemic steroids but not to antibiotics, and lesions heal leaving papery scars.

The skin changes of pregnancy

Physiological

A darkening of the nipples, genitals, and of a line down the centre of the abdominal wall, is often accompanied by a generalized increase in skin pigmentation. Sebum excretion may increase. Spider naevi and palmar erythema are both common in pregnancy, and are caused by high oestrogen levels. Stretch marks and skin tags are common too.

Dermatoses of pregnancy

Itching is common in pregnancy, usually for obvious reasons such as scabies, but sometimes in association with mild cholestasis. The terminology of the more striking itchy dermatoses of pregnancy has always been confusing. We now prefer to divide them into only three main categories.

1 Pruritic urticarial papules and plaques of pregnancy (PUPP) (Fig. 19.18). This usually starts in the third trimester. The urticated lesions favour the abdomen, particularly in association with stretch marks. The cause of PUPP is not known, but it is not associated with danger to the unborn child, and clears after the child is born. Treatment is symptomatic.

2 Prurigo of pregnancy. The development of many excoriated papules, which are not urticated, starts rather earlier than PUPP. It also carries no threat to the unborn child and clears after the child is born.

3 Pemphigoid gestationis is rare, and triggered by HLA differences between the mother and the fetus. However, the autoantibodies are directed at the same antigens as those of ordinary pemphigoid (p. 111). The condition may start at any time during pregnancy, or even just after childbirth, tending to start earlier in subsequent pregnancies. The itchy urticarial plaques, often annular, go on to blister. Immunofluorescence differentiates the condition from PUPP. Systemic corticosteroids are usually required, and there may be a risk of premature delivery.

Effect of pregnancy on other dermatoses

Candidiasis is common in pregnancy and genital warts can become unusually luxuriant. Podophyllin should be avoided for the latter as it may be toxic to the fetus. The effects of pregnancy on common disorders, such as atopic eczema, acne and psoriasis, are unpredictable in any individual patient, but there is an overall trend towards improvement.

Further reading

Most people accept that there are strong links between skin disease and the emotions, but only a few skin disorders, such as dermatitis artefacta, have emotional factors as their direct cause. The relationships between the mind and the skin are usually subtler and more complex than this. Nevertheless, patients with skin disorders do have a higher prevalence of psychiatric abnormalities than the general population, although specific personality profiles and disorders can seldom be tied to specific skin diseases. Similarly, it is still not clear how, or even how often, psychological factors trigger, worsen or perpetuate such everyday problems as atopic eczema or psoriasis.

Each school of psychiatry has its own theories on the subject, but their explanations do not satisfy everyone. Do people really damage their skin to satisfy guilt feelings? Does their skin ‘weep’ because they have themselves suppressed weeping? Until more is known, it may be wise to adopt a simpler and more pragmatic approach, in which interactions between the skin and psyche are divided into two broad groups:

- emotional reactions to the presence of skin disease, real or imagined; and
- the effects of emotions on skin disease (Fig. 20.1).

**Reactions to skin disease**

The presence of disfiguring skin lesions can distort the emotional development of a child: some become withdrawn, others become aggressive, but many adjust well. The range of reactions to skin disease is therefore wide. At one end lies indifference to grossly disfiguring lesions and, at the other, lies an obsession with skin that is quite normal. Between these extremes are reactions ranging from natural anxiety over ugly skin lesions to disproportionate worry over minor blemishes.

A chronic skin disease such as psoriasis can undoubtedly spoil the lives of those who suffer from it. It can interfere with work, and with social activities of all sorts including sexual relationships, causing sufferers to feel like outcasts. The heavy drinking of so many men with severe psoriasis is one result of these pressures. An experienced dermatologist will be on the lookout for depression and the risk of suicide, as up to 10% of patients with psoriasis have had suicidal thoughts. However, these reactions do not necessarily correlate with the extent and severity of the eruption as judged by an outside observer. Who has the more disabling problem: someone with 50% of his body surface covered in psoriasis, but who largely ignores this and has a happy family life and a productive job, or one with 5% involvement whose social life is ruined by it? The concept of ‘body image’ is useful here.
Body image

All of us think we know how we look, but our ideas may not tally with those of others. The nose, face, hair and genitals tend to rank high in a person’s ‘corporeal awareness’, and trivial lesions in those areas can generate much anxiety. The facial lesions of acne, for example, can lead to a huge loss of self-esteem.

Dermatological delusional disease

Dysmorphophobia

This is the term applied to distortions of the body image. Minor and inconspicuous lesions are magnified in the mind to grotesque proportions.

Dermatological ‘non-disease’

This is a form of dysmorphobia. The clinician can find no skin abnormality, but the distress felt by the patient leads to anxiety, depression or even suicide. Such patients are not uncommon. They expect dermatological solutions for complaints such as hair loss, or burning, itching and redness of the face or genitals. The dermatologist, who can see nothing wrong, cannot solve matters and no treatment seems to help. Such patients are reluctant to see a psychiatrist although some may suffer from a monosymptomatic hypochondriacal psychosis.

Other delusions

These patients sustain single hypochondriacal delusions for long periods, in the absence of other recognizable psychiatric disease. Some are eccentric and live in social isolation. Some believe that they have syphilis, AIDS or skin cancer. In dermatology, many of these patients have the delusion that their skin is infested with parasites.

Delusions of parasitosis (Fig. 20.2)

This term is better than ‘parasitophobia’, which implies a fear of becoming infested. Patients with delusions of parasitosis are unshakably convinced that they are already infested. No rational argument can convince them that they are not; the pest control agencies that they have called in, and their medical advisers therefore must both be wrong. Symptoms include odd sensations of crawling and biting, and patients often bring to the clinic a box of specimens of the ‘parasite’ at different stages of its supposed life cycle. These must be examined microscopically but usually turn out to be fragments of skin, hair, clothing, haemorrhagic crusts or unclassifiable debris. The skin changes may include gouge marks and scratches, but it is convenient to consider these patients separately from those with dermatitis artefacta.

These patients become angry if doubts are cast on their ideas, or if they are referred to a psychiatrist. How could treatment for mental illness possibly be expected to kill parasites? Family members may share their delusions and much tact is needed to secure any cooperation with treatment. Direct confrontations are best avoided; sometimes it may be best simply to treat with psychotropic drugs, explaining that these may be able to help some of the symptoms.

The delusions of a few of these patients are based on an underlying depression or schizophrenia, and of a further few on organic problems such as vitamin deficiency or cerebrovascular disease. These disorders must be treated on their own merits. However, most patients suffer from monosymptomatic hypochondriacal delusions, which can often be suppressed by treatment with drugs, accepting that these will be needed long-term. Otherwise, the outlook for resolution is poor. Pimozide was once the most popular treatment for this condition but high doses carry cardiac risks. If pimozide is used, an electrocardiogram (ECG) should be performed before starting treatment and the drug should not be given to those with a prolonged Q-T interval or with a history of cardiac dysrhythmia. Patients on pimozide in excess of 16 mg daily need periodic ECG checks. Tardive dyskinesia may develop and persist despite withdrawal of the drug. Risperidone, olanzapine and sulpiride are reasonable, and perhaps safer, alternatives. Some patients gain insight and relief. Others hint that their parasites still persist although this no longer disables them.

Dermatitis artefacta

Here the skin lesions are caused and kept going by the patient’s own actions, but parasites are not held to be to blame. Patients with dermatitis artefacta deny self-trauma but, naturally, if treatment is left to them to carry out, their problems do not improve. Lesions will
heal under occlusive dressings, but this does not alter the underlying psychiatric problems, and lesions may recur or crop up outside the bandaged areas. Different types of dermatitis artefacta are listed in Table 20.1.

The lesions favour accessible areas, and do not fit with known pathological processes. The diagnosis is often difficult to make, but an experienced clinician will suspect it because there are no primary lesions and because of the bizarre shape or grouping of the lesions, which may be rectilinear or oddly grouped (Fig. 20.3). Areas damaged by burning (Fig. 20.4), corrosive chemicals (Fig. 20.5), or by digging have their own special appearance.

More subtle changes are seen in ‘dermatological pathomimicry’, in which patients reproduce or aggravate their skin disease by deliberate contact with materials to which they know they will react.

**Table 20.1** Types of dermatitis artefacta.

<table>
<thead>
<tr>
<th>Type</th>
<th>Personality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor habits, e.g. excoriated acne</td>
<td>Relatively normal</td>
</tr>
<tr>
<td>More obvious lesions</td>
<td>Hysterical or neurotic (secondary gain)</td>
</tr>
<tr>
<td>Bizarre</td>
<td>Psychotic</td>
</tr>
<tr>
<td>Malingering</td>
<td>Criminal</td>
</tr>
</tbody>
</table>

Fig. 20.2 Delusions of parasitosis—the sequence of events.
Neurotic excoriations

Patients with neurotic excoriations differ from those with other types of dermatitis artefacta in that they admit to picking and digging at their skin. This habit affects women more often than men and is most active at times of stress. The clinical picture is mixed, with crusted excoriations and pale scars, often with a hyperpigmented border, lying mainly on the face, neck, shoulders and arms (Fig. 20.6). The condition may last for years and psychiatric treatment is seldom successful.

LEARNING POINTS

1. Do not reward a delusion with a treatment for scabies.
2. Direct confrontations with patients with dermatitis artefacta or delusions of parasitosis may make you feel better, but do little for them.

Neurotic excoriations

Apart from frank malingerers, the patients are often young women with some medical knowledge, perhaps a nurse. Some form of ‘secondary gain’ from having skin lesions may be obvious. The psychological problems may be superficial and easily resolved, but sometimes psychiatric help is needed and the artefacts are part of a prolonged psychiatric illness. A few patients respond to banal treatments if given the chance to save face. Direct confrontation and accusations are usually best avoided, and the condition may last for some years.
Acne excoriée

Here the self-inflicted damage is based to some extent on the lesions of acne vulgaris, which may in themselves be mild, but become disfiguring when dug and squeezed to excess. The patients are usually young girls who may leave themselves with ugly scars. A psychiatric approach is often unhelpful and a daily ritual of attacking the lesions, helped by a magnifying mirror, may persist for years.

Localized neurodermatitis (lichen simplex)

This term refers to areas of itchy lichenification, perpetuated by bouts of scratching in response to stress. The condition is not uncommon and can occur on any area of skin. In men, lesions are often on the calves; in women, they favour the nape of the neck where the redness and scaling look rather like psoriasis. Some examples of persistent itching in the anogenital area are caused by lichen simplex there.

Patients with localized neurodermatitis develop scratch responses to minor itch stimuli more readily than controls. Local therapy does not alter the underlying cause, but topical steroids, sometimes only the most potent ones, ameliorate the symptoms. Occlusive bandaging of suitable areas clears only those lesions that are covered.

Hair-pulling habit

Trichotillomania is too dramatic a word for what is usually only a minor comfort habit in children, ranking alongside nail-biting and lip-licking. Perhaps the term should be dropped in favour of ‘hair-pulling habit’. It is usually of little consequence, and children who twist and pull their hair, often as they are going to sleep, seldom have major psychiatric disorders. The habit often goes away most quickly if it is ignored. However, more severe degrees of hair-pulling are sometimes seen in disturbed adolescents and in those with learning difficulties; then the outlook for full regrowth is less good, even with formal psychiatric help.

The diagnosis can usually be made on the history, but some parents do not know what is going on. The bald areas do not show the exclamation-mark hairs of alopecia areata, or the scaling and inflammation of scalp ringworm. The patches are irregular in outline and hair loss is never complete. Those hairs that remain are bent or broken, and of variable length.
**Dermatoses precipitated or perpetuated by emotional factors**

Popular candidates for inclusion in this group of diseases are psoriasis, urticaria, atopic eczema, pompholyx, discoid eczema, alopecia areata, lichen simplex and lichen planus. Fancy rather than fact still rules here, but a scientific basis for these effects is gradually being established. For example, in psoriasis, stress increases the neuropeptide content of lesions, with a concomitant drop in the activity of enzymes that degrade neuropeptides, especially mast-cell chymase. In addition, the blood concentrations of certain neuromediators, especially β-endorphin, changes during exacerbations. Yet an aura of doubt lingers on—for a variety of reasons. The concept of stress is not a simple one, and the terms in which it is discussed are sometimes used rather vaguely. Each type of stress may well provoke its own pattern of response. For this reason many investigators have preferred to record damaging life events rather than to speculate about the presence of stress itself. However, there are problems with this approach too, as a barrage of minor daily annoyances may well be more important than major life events. Every dermatologist will have seen apparent examples of associations between external stress and exacerbations of most of these conditions, but proof that stress causes them is hard to find. Some studies suggest that even hyperhidrosis of the palms and soles, once thought to be an accentuated response to stress, has no relationship to chronic anxiety at all. No one questions that stress can cause sweating of the palms, but some studies suggest that chronic hyperhidrosis of the palms and soles, once thought to be simply an accentuated response to stress, has no relationship to chronic anxiety at all.

**Further reading**


The human genome consists of 23 pairs of chromosomes carrying an estimated 30 000 genes. The pairs of matching chromosomes as seen at colchicine-arrested metaphase are numbered in accordance with their size. A centromere divides each chromosome into a shorter (p) and a longer (q) arm.

Any individual’s chromosomal make-up (karyotype) can be expressed as their total number of chromosomes plus their sex chromosome constitution. A normal male therefore is 46XY. A shorthand notation exists for recording other abnormalities such as chromosome translocations and deletions.

The precise location of any gene can be given by naming the chromosome, the arm of the chromosome (p or q), and the numbers of the band and subband of the chromosome, as seen with Giemsa staining, on which it lies. One of the genes important for atopy, for instance, lies on chromosome 11q13, i.e. on the long arm of chromosome 11 at band 13.

Several techniques can be used to identify the position of a gene.
1 A clue maybe offered by finding that some affected individuals have chromosomal deletions or unbalanced translocations, suggesting that the gene in question lies on the abnormal segments.
2 Linkage analysis. Genes are linked if they lie close together on the same chromosome; they will then be inherited together. The closer together they are, the less is the chance of their being separated by crossovers, one to six of which, depending on length, occur on each chromosome at meiosis. Each member of an affected family has to be examined both for the presence of the trait to be mapped, and also for a marker, usually a DNA probe, which has already been mapped. If linkage is established then the two loci will be close on the same chromosome. The probability of the results of such a study representing true linkage can be expressed as a logarithm of the odds (Lod) score. A score of three or more suggests that the linkage is likely to be genuine.
3 Somatic cell hybridization. A hybrid made by fusing a human cell with a mouse cell will at first have two sets of chromosomes. Later human chromosomes are lost randomly until a stable state is reached. Those cells that produce a particular human protein must contain the relevant chromosome. A panel of such hybrid cells can be created which differ in their content of human chromosomes. By comparing these, the chromosomal site of the relevant gene can be deduced.
4 In situ hybridization. A cloned sequence of DNA, if made single-stranded by heat, will anneal to its complementary sequence on a chromosome. Radioactive or fluorescent labelling can be used to indicate its position there.

Non-Mendelian genetics

Traditional genetics has also been extended by the introduction of several new non-Mendelian concepts of importance in dermatology. These include the following.
1 Mosaicism. A mosaic is a single individual made up of two or more genetically distinct cell lines. The concept is important in several skin disorders including incontinentia pigmenti (p. 305) and segmental neurofibromatosis (p. 302). The mutation of a single cell in a fetus (a postzygotic mutation) may form a clone of abnormal cells. In the epidermis these often adopt a bizarre pattern of lines and whorls—Blaschko’s lines, named after the dermatologist who recorded them in linear epidermal naevi in 1901.
2 Contiguous gene deletions. Complex phenotypes occur when several adjacent genes are lost. In this way,
for example, X-linked ichthyosis may associate with hypogonadism or anosmia.

3 Genomic imprinting means that genes may differ in their effect depending on the parent from which they are inherited. Genes from the father seem especially important in psoriasis, and from the mother in atopy (p. 82).

4 Uniparental disomy occurs when both pairs of genes are derived from the same parent so that an individual lacks either a maternal or a paternal copy. In this way a disorder usually inherited as a recessive trait can arise even though only one parent is a carrier.

Inheritance is important in many of the conditions discussed in other chapters and this has been highlighted in the sections on aetiology. This chapter includes some genetic disorders not covered elsewhere.

**Neurofibromatosis**

This relatively common disorder affects about 1 in 3000 people and is inherited as an autosomal dominant trait. There are two main types: von Recklinghausen’s neurofibromatosis (NF1; which accounts for 85% of all cases) and bilateral acoustic neurofibromatosis (NF2); these are phenotypically and genetically distinct.

**Cause**

The NF1 gene has been localized to chromosome 17q11.1. It is unusually large (300 kb) and many different mutations within it have now been identified. The NF1 gene is a tumour suppressor gene, the product of which, neurofibromin, interacts with the product of the RAS proto-oncogene. This may explain the susceptibility of NF1 patients to a variety of tumours. The inheritance of NF1 is as an autosomal dominant trait but about one-half of index cases have no preceding family history.

The inheritance of NF2 is also autosomal dominant. Mapping to chromosome 22q12.2 followed the observation of changes in chromosome 22 in meningiomas as these tumours may be seen in NF2. This gene also normally functions as a tumour-suppressor gene, the product of which is known as schwannomin.

**Clinical features**

The physical signs include the following.

**Von Recklinghausen’s neurofibromatosis (NF1)**

- Six or more café au lait patches (light brown oval macules; Fig. 21.1), usually developing in the first year of life.
- Axillary freckling (Fig. 21.2) in two-thirds of affected individuals.
- Variable numbers of skin neurofibromas, some small and superficial, others larger and deeper, ranging from flesh-coloured to pink, purple or brown (Fig. 21.1). Most are dome-like nodules, but others are irregular raised plaques. Some are firm, some soft and compressible through a deficient dermis (‘button-hole’ sign); others feel ‘knotty’ or ‘wormy’. Neurofibromas may not appear until puberty and become larger and more numerous with age.
- Small circular pigmented hamartomas of the iris (Lisch nodules; Fig. 21.3), appear in early childhood.

Nearly all NF1 patients meet the criteria for diagnosis by the age of 8 years, and all do so by 20 years. The usual order of appearance of the clinical features is café au lait macules, axillary freckling, Lisch nodules and neurofibromas.
the skin neurofibromas. A segmental form of NF1 is caused by a postzygotic mutation. Isolated neurofibromas are not uncommon in individuals without neurofibromatosis and are of little consequence unless they are painful.

Complications

**Von Recklinghausen’s neurofibromatosis**

A neurofibroma will occasionally change into a neurofibrosarcoma. Other associated features may include kyphoscoliosis, mental deficiency, epilepsy, renal artery stenosis and an association with phaeochromocytoma. Forme fruste variants occur, e.g. segmental neurofibromatosis.

**Bilateral acoustic neurofibromatosis**

Other tumours of the central nervous system may occur, especially meningiomas and gliomas.

Management

Ugly or painful lesions, and any suspected of undergoing malignant change, should be removed. The chance of a child of an affected adult developing the disorder is 1 in 2—parents should be advised about this.

**Tuberous sclerosis**

This uncommon condition, with a prevalence of about 1 in 12 000 in children under 10 years, is also inherited as an autosomal dominant trait, with variable expressivity even within the same family. As fertility is reduced, transmission through more than two generations is rare.

Cause

Mutations at two different loci can, independently, cause clinically identical tuberous sclerosis. The product of one gene (TSC1), lying at 9q34, is hamartin; that encoded by the other gene (TSC2) is tuberin. Both are associated in vivo, and probably act in the same biological pathways as tumour suppressors. TSC1 gene mutations are responsible for a minority of cases and are under-represented in sporadic cases.
Clinical features

The skin changes include the following.
- **Small oval white patches** (‘ash leaf macules’) occur in 80% of those affected. These are important as they may be the only manifestation at birth.
- **Adenoma sebaceum** occur in 85% of those affected. They develop at puberty as pink or yellowish acne-like papules on the face, often around the nose (Fig. 21.4).
- **Peri-ungual fibromas** occur in 50% of patients. These develop in adult life as small pink sausage-like lesions emerging from the nail folds (Fig. 21.5).
- **Connective tissue naevi** (‘shagreen patches’) are seen in 40% of patients. Cobblestone, somewhat yellow plaques often arise in the skin over the base of the spine.

Other features may include:
- epilepsy (in 75% of patients);
- mental retardation (in 50% of patients);
- ocular signs, including retinal phakomas and pigmentary abnormalities (in 50% of patients);
- hyperplastic gums;
- gliomas along the lateral walls of the lateral ventricles (80% of cases) and calcification of the basal ganglia; and
- renal and heart tumours.

Diagnosis and differential diagnosis

Any baby with unexplained epilepsy should be examined with a Wood’s light (p. 33) to look for ash leaf macules. Skull X-rays and computer assisted tomography scans (Fig. 21.6) help to exclude involvement of the central nervous system and kidneys.
Chapter 21

The skin is normal at birth. Multiple freckles, roughness and keratoses on exposed skin appear between the ages of 6 months and 2 years (Fig. 21.7). Photosensitivity increases thereafter. The atrophic facial skin shows telangiectases and small angiomas. Many tumours develop on light-damaged skin: these include basal cell carcinomas, squamous cell carcinomas, keratoacanthomas and malignant melanomas. Many patients die before the age of 20 years. Eye problems are common and include photophobia, conjunctivitis and ectropion. The condition may be associated with microcephaly, mental deficiency, dwarfism, deafness and ataxia (De Sanctis–Cacchione syndrome).

Diagnosis

This becomes evident on clinical grounds, although variants with minor signs may cause difficulty. The DNA repair defect can be detected in a few laboratories after the ultraviolet irradiation of cultured fibroblasts or lymphocytes from the patient.

Treatment

Skin cancers can be prevented by strict avoidance of sunlight, the use of protective clothing, wide-brimmed hats and of reflectant sunscreens and dark glasses. If possible, patients should not go out by day. Early and
complete removal of all tumours is essential. Radiotherapy should be avoided.

Incontinentia pigmenti

This rare condition is an X-linked dominant disorder, usually lethal before birth in males. The gene for familial cases has been mapped to Xq28 and that for the more severe sporadic cases to Xp11. The bizarre patterning of the skin is caused by random X-inactivation (Lyonization). The lines of affected and normal skin represent clones of cells in which either the abnormal or normal X chromosome is active.

Clinical features

There are three stages in the evolution of the skin signs.
1. **Vesicular.** Linear groups of blisters occur more on the limbs than trunk.
2. **Warty.** After a few weeks the blisters dry up and the predominant lesions are papules with a verrucous hyperkeratotic surface.
3. **Pigmented.** A whorled or ‘splashed’ macular pigmentation, ranging from slate-grey to brown, replaces the warty lesions. Its bizarre patterning is a strong diagnostic pointer.

Occasionally, the vesicular and warty stages occur in utero; warty or pigmented lesions may therefore be the first signs of the condition. There is also a variant in which pale rather than dark whorls and streaks are seen.

Associated abnormalities are common. One-quarter of patients have defects of their central nervous system, most commonly mental retardation, epilepsy or microcephaly. Skull and palatal abnormalities may also be found. Delayed dentition, and even a total absence of teeth, are recognized features. The incisors may be cone- or peg-shaped. Ocular defects occur in one-third of patients, the most common being strabismus, cataract and optic atrophy.

Differential diagnosis

Diagnosis is usually made in infancy when bullous lesions predominate so the differential diagnosis includes bullous impetigo (p. 190), candidiasis (p. 38), and the rarer linear immunoglobulin A (IgA) bullous disease of childhood (p. 113) and epidermolysis bullosa (p. 116).

Investigations

There is frequently an eosinophilia in the blood. Biopsy of an intact blister reveals an intraepidermal vesicle filled with eosinophils.

Management

This is symptomatic and includes measures to combat bacterial and candidal infection during the vesicular phase. Family counselling should be offered.

Ehlers–Danlos syndrome

Eleven subtypes are now recognized and this complicated subject has earned its own scientific group, which continuously updates classification and molecular biology.

Cause

All varieties of the Ehlers–Danlos syndrome are based on abnormalities in the formation or modification of collagen and the extracellular matrix, but are not necessarily a result of mutations in the collagen genes themselves. Established defects include lysyl hydroxylase deficiency, abnormalities in pro-alpha-1 (V) collagen chains, mutations in type III collagen genes, a deficiency of procollagen protease, and a fibronectin defect.

Clinical features

- Hyperelasticity of the skin.
- Hyperextensibility of the joints.
- Fragility of skin and blood vessels.
- Easy bruising.
- Curious (‘cigarette paper’) scars.

Complications

These depend on the type. They include subluxation of joints, varicose veins in early life, an increased...
liability to develop hernias, kyphoscoliosis, aortic aneurysms and ruptured large arteries, and intraocular haemorrhage. Affected individuals may be born prematurely as a result of the early rupture of fragile fetal membranes.

**Diagnosis and treatment**

The diagnosis is made on the clinical features and family history. The frequent skin lacerations and prominent scars may suggest child abuse. The diagnosis and type can sometimes be confirmed by enzyme studies on isolated fibroblasts. There is no effective treatment but genetic counselling is needed.

**Pseudoxanthoma elasticum**

This is the classical inherited connective tissue disorder affecting the elastic structures in the body—most obviously in the skin, blood vessels and eyes.

**Cause**

It has recently been found that both the dominantly and recessively inherited types are a result of mutations in a gene (on chromosome 16p13.1) encoding for a transmembrane transporter protein, which is a member of the ABC transporters superfamily. It is still not clear how this causes the disease.

**Pathology**

The elastic fibres in the mid-dermis become swollen and fragmented; their calcification is probably a secondary feature. The elastic tissue of blood vessels and of the retina may also be affected.

**Clinical features**

The skin of the neck and axillae, and occasionally of other body folds, is loose and wrinkled. Groups of small yellow papules give these areas a ‘plucked chicken’ appearance (Fig. 21.8). Breaks in the retina show as angioid streaks, which are grey poorly defined areas radiating from the optic nerve head. Arterial involvement may lead to peripheral, coronary or cerebral arterial insufficiency.

Fig. 21.8 The ‘plucked chicken’ appearance of pseudoxanthoma in the antecubital fossa.

**LEARNING POINT**

In all genodermatoses, the decision to have children, or not, must lie with the family concerned. Make sure they have all of the facts before them.

**Complications**

The most important are hypertension, recurrent gut haemorrhages, ischaemic heart disease and cerebral haemorrhage.

**Diagnosis and treatment**

The diagnosis is made clinically and confirmed by the histology. There is no effective treatment.

**Further reading**

Almost any drug can cause a cutaneous reaction, and many inflammatory skin conditions can be caused or exacerbated by drugs. A drug reaction can reasonably be included in the differential diagnosis of most skin diseases.

**Mechanisms**

These are many and various (Table 22.1), being related both to the properties of the drug in question and to a variety of host factors. Indeed, pharmaceutical companies study genes to predict responders and non-responders, and to detect patients who may be unable to metabolize a drug normally. For example, drug-induced lupus erythematosus occurs more commonly among ‘slow acetylators’ who take hydralazine. However, not all adverse drug reactions have a genetic basis; the excess of drug eruptions seen in the elderly may reflect drug interactions associated with their high medication intake.

**Non-allergic drug reactions**

Not all drug reactions are based on allergy. Some are a result of overdosage, others to the accumulation of drugs, or to unwanted pharmacological effects, e.g. stretch marks from systemic steroids (Fig. 22.1). Other reactions are idiosyncratic (an odd reaction peculiar to one individual), or a result of alterations of ecological balance (see below).

Cutaneous reactions can be expected from the very nature of some drugs. These are normal but unwanted responses. Patients show them when a drug is given in a high dose, or even in a therapeutic dose. For example, mouth ulcers frequently occur as a result of the cytotoxicity of methotrexate. Silver-based preparations, given for prolonged periods, can lead to a slate-grey colour of the skin (argyria). Acute vaginal candidiasis occurs when antibiotics remove the normal resident bacteria from the female genital tract and so foster colonization by yeasts. Dapsone or rifampicin, given to patients with lepromatous leprosy, may cause erythema nodosum leprosum as the immune response to the bacillus is re-established.

<table>
<thead>
<tr>
<th>Table 22.1 Some mechanisms involved in drug reactions.</th>
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<tbody>
<tr>
<td>Pharmacological</td>
</tr>
<tr>
<td>Caused by overdosage or failure to excrete or metabolize</td>
</tr>
<tr>
<td>Cumulative effects</td>
</tr>
<tr>
<td>Altered skin ecology</td>
</tr>
<tr>
<td>Allergic</td>
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<tr>
<td>IgE-mediated</td>
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<td>Cytotoxic</td>
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<td>Immune complex-mediated</td>
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<tr>
<td>Cell-mediated</td>
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<tr>
<td>Idiosyncratic</td>
</tr>
<tr>
<td>Exacerbation of pre-existing skin conditions</td>
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</tbody>
</table>

Fig. 22.1 Gross striae caused by systemic steroids.
Non-allergic reactions are often predictable. They affect many, or even all, patients taking the drug at a sufficient dosage for a sufficient time. Careful studies before marketing should indicate the types of reaction that can be anticipated.

**Allergic drug reactions**

Allergic drug reactions are less predictable. They occur in only a minority of patients receiving a drug and can do so even with low doses. Allergic reactions are not a normal biological effect of the drug and usually appear after the latent period required for an immune response. Chemically related drugs may cross-react.

Fortunately, allergic drug reactions present in only a limited number of forms, namely urticaria and angioedema, vasculitis, erythema multiforme, or a morbilliform erythema. Rarer allergic reactions include bullae, erythroderma, pruritus, toxic epidermal necrolysis and the hypersensitivity syndrome reaction. This syndrome includes the triad of fever, rash (from morbilliform to exfoliative dermatitis) and internal involvement (hepatitis, pneumonitis, nephritis and haematological abnormalities).

**Presentation**

**Some drugs and the reactions they can cause**

Experience helps here, together with a knowledge of the reactions most likely to be caused by individual drugs, and also of the most common causes of the various reaction patterns. Any unusual rash should be suspected of being a drug reaction, and approached along the lines listed in Table 22.2.

**Antibiotics**

Penicillins and sulphonamides are among the drugs most commonly causing allergic reactions. These are often morbilliform (Fig. 22.2), but urticaria and erythema multiforme are common too. Viral infections are often associated with exanthems, and many rashes are incorrectly blamed on an antibiotic when, in fact, the virus was responsible. Most patients with infectious mononucleosis develop a morbilliform rash if ampicillin is administered. Penicillin is a common cause of severe anaphylactic reactions, which can be life-threatening. Minocycline can accumulate in the tissues and produce a brown or grey colour in the mucosa, sun-exposed areas or at sites of inflammation, as in the lesions of acne. Minocycline can rarely cause the hypersensitivity syndrome reaction, hepatitis, worsen lupus erythematosus, or elicit a transient lupus-like syndrome.

**Penicillamine**

Like penicillin itself, this can cause morbilliform eruptions or urticaria, but the drug has also been incriminated as a cause of haemorrhagic bullae at sites of inflammation.
Some common reaction patterns and drugs which can cause them

**Toxic (reactive) erythema**

This vague term describes the most common type of drug eruption, looking sometimes like measles or scarlet fever, and sometimes showing prominent urticarial Fig. 22.4) or erythema multiforme-like elements. Itching and fever may accompany the rash. Culprits include antibiotics (especially ampicillin), sulphonamides and related compounds (diuretics and hypoglycaemics), barbiturates, phenylbutazone and para-aminosalicylate (PAS).

**Oral contraceptives**

Reactions to these are less common now that their hormonal content is small. The hair fall that may follow stopping the drug is like that seen after pregnancy (telogen effluvium; p. 168). Chloasma, hirsutism, erythema nodosum, acne and photosensitivity are other reactions.

**Gold**

This frequently causes rashes. Its side-effects range from pruritus to morbilliform eruptions, to curious papulosquamous eruptions such as pityriasis rosea or lichen planus. Erythoderma, erythema nodosum, hair fall and stomatitis may also be provoked by gold.

**Steroids**

Cutaneous side-effects from systemic steroids include a ruddy face, cutaneous atrophy, striae (Fig. 22.1), hirsutism, an acneiform eruption and a susceptibility to cutaneous infections, which may be atypical.

**Anticonvulsants**

There may be cross-reactivity between phenytoin, carbamazepine and phenobarbitol. Skin reactions are common and include erythematous, morbilliform, urticarial and purpuric rashes. Toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, the hypersensitivity syndrome reaction and a lupus erythematosus-like syndrome are rare. A phenytoin-induced pseudolymphoma syndrome has also been described in which fever and arthralgia are accompanied by generalized lymphadenopathy and hepatosplenomegaly and, sometimes, some of the above skin signs. Long-term treatment with phenytoin may cause gingival hyperplasia (Fig. 22.3) and coarsening of the features as a result of fibroblast proliferation.

**Highly active antiretroviral drugs**

The long-term use of highly active antiretroviral drugs (HAART) has been commonly associated with lipodystrophy, producing a gaunt facies with sunken cheeks.
indomethacin (indometacin), phenytoin and oral contraceptives are among the possible causes.

**Erythema multiforme** (Chapter 8)

Target-like lesions appear mainly on the extensor aspects of the limbs, and bullae may form. In the Stevens–Johnson syndrome, the patients are often ill and the mucous membranes are severely affected. Sulphonamides, barbiturates, lamotrigine and phenylbutazone are known offenders.

**Purpura**

The clinical features are seldom distinctive apart from the itchy brown petechial rash on dependent areas that is characteristic of carbromal reactions. Thrombocytopenia and coagulation defects should be excluded (Chapter 11). Thiazides, sulphonamides, phenylbutazone, sulphonylureas, barbiturates and quinine are among the drugs reported to cause purpura.

**Bullous eruptions**

Some of the reactions noted above can become bullous. Bullae may also develop at pressure sites in drug-induced coma.

**Eczema**

This is not a common pattern and occurs mainly when patients sensitized by topical applications are given the drug systemically. Penicillin, sulphonamides, neomycin, phenothiazines and local anaesthetics should be considered.

**Exfoliative dermatitis**

The entire skin surface becomes red and scaly. This can be caused by drugs (particularly phenylbutazone, PAS, isoniazid and gold), but can also be caused by widespread psoriasis and eczema.

**Fixed drug eruptions**

Round, erythematous or purple, and sometimes bullous plaques recur at the same site each time the drug

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**Fig. 22.5** The cause, clinical features and treatment of anaphylaxis.
Toxic epidermal necrolysis (p. 115)

In adults, this ‘scalded skin’ appearance is usually drug-induced (e.g. sulphonamides, barbiturates, phenylbutazone, oxyphenbutazone, phenytoin, carbamazepine, lamotrigine or penicillin).

Hair loss

This is a predictable side-effect of acitretin and cytotoxic agents, an unpredictable response to some anticoagulants, and sometimes seen with antithyroid drugs. Diffuse hair loss may occur during, or just after, the use of an oral contraceptive.

Hypertrichosis

This is a dose-dependent effect of diazoxide, minoxidil and cyclosporin A.

Pigmentation (see also p. 252)

Chloasma (p. 251) may follow an oral contraceptive plus sun exposure. Large doses of phenothiazines impart a blue-grey colour to exposed areas (Fig. 22.7); heavy metals can cause a generalized browning;
clofazimine makes the skin red; mepacrine turns the skin yellow; and minocycline turns leg skin a curious greenish grey colour that suggests a bruise.

Photosensitivity

This is dealt with in Chapter 16. Always exclude the common drug causes (thiazides, tetracyclines, phenothiazines, sulphonamides or psoralens).

Xerosis

The skin can become rough and scaly in patients receiving oral retinoids, nicotinic acid or lithium.

Exacerbation of pre-existing skin conditions

Psoriasis and acne are good examples of this. Psoriasis may be made worse by giving β-blockers, antimalarials, terbinafine or lithium. Glucocorticoids, progesterone, androgens, anticonvulsants, bromides, iodiums and lithium may exacerbate acne.

Course

The different types of reaction vary so much that a brief summary is not possible. If a reaction occurs during the first course of treatment, it characteristically begins late, often about the ninth day, or even after the drug has been stopped. In such cases, it has taken that lag time to induce an immune reaction. In previously exposed patients the common morbilliform allergic reaction starts 2–3 days after the administration of the drug. The speed with which a drug eruption clears depends on the type of reaction and the rapidity with which the drug is eliminated.

Differential diagnosis

The differential diagnosis ranges over the whole subject of dermatology depending on which disease is mimicked. For instance, toxic erythema reactions can look very like measles, pityriasis rosea or even secondary syphilis. The general rule is never to forget the possibility of a drug eruption when an atypical rash is seen. Six vital questions should be asked (Table 22.2).

Treatment

The first approach is to withdraw the suspected drug, accepting that several drugs may need to be stopped at the same time. This is not always easy as sometimes a drug is necessary and there is no alternative available. At other times the patient may be taking many drugs and it is difficult to know which one to stop. The decision to stop or continue a drug depends upon the nature of the drug, the necessity of using the drug for treatment, the availability of chemically unrelated alternatives, the severity of the reaction, its potential reversibility, and the probability that the drug is actually causing the reaction.

Assessment depends upon clinical detective work (Table 22.2). Judgements must be based on probabilities and common sense. Every effort must be made to correlate the onset of the rash with prescription records. Often, but not always, the latest drug to be introduced is the most likely culprit. Prick tests and in vitro tests for allergy are still too unreliable to be of value. Re-administration, as a diagnostic test, is usually unwise except when no suitable alternative drug exists.

Non-specific therapy depends upon the type of eruption. In urticaria, antihistamines are helpful. In some reactions, topical or systemic corticosteroids can be used, and applications of calamine lotion may be soothing.

Anaphylactic reactions require special treatment (Fig. 22.4) to ensure that the airway is not compromised (e.g. oxygen, assisted respiration or even emergency tracheostomy). One or more injections of adrenaline (epinephrine) (1 : 1000) 0.5–0.5 mL should be given subcutaneously or intramuscularly in adults before the slow (over 1 min) intravenous injection of chlorphenamine maleate (10–20 mg diluted in syringe

LEARNING POINTS

1 This whole chapter is a warning against polypharmacy. Do your patients really need all the drugs they are taking?
2 If you suspect a drug eruption, keep on going back to the history.
3 Watch out for eruptions from new drugs.
4 Avoid provocation tests unless there are very strong indications for them.
with 5–10 mL of blood). Although the action of intravenous hydrocortisone (100 mg) is delayed for several hours it should be given to prevent further deterioration in severely affected patients. Patients should be observed for 6 h after their condition is stable, as late deterioration may occur. If an anaphylactic reaction is anticipated, patients should be taught how to self-inject adrenaline, and may be given a salbutamol inhaler to use at the first sign of the reaction.

To re-emphasize, the most important treatment is to stop the responsible drug. Desensitization, seldom advisable or practical, may rarely be carried out when therapy with the incriminated drug is essential and when there is no suitable alternative (e.g. with some anticonvulsants, antituberculous and antileprotic drugs). An expert, usually a physician with considerable experience of the drug concerned, should supervise desensitization.

**Further reading**


An accurate diagnosis, based on a proper history and examination (Chapter 3), must come before a rational line of treatment can be chosen; even when a firm diagnosis has been reached, each patient must be treated as an individual. For some, no treatment may even be the best treatment, especially when the disorder is cosmetic or if the treatment would be worse than the condition itself. A patient with minimal vitiligo, for example, may be helped more by careful explanation and reassurance than by prescriptions.

If a diagnosis cannot be reached, the doctor has to decide whether a specialist opinion is needed, or whether it is best to observe the rash, perhaps treating it for a while with a bland application. In either case, the indiscriminate use of topical steroids or other medications, in the absence of a working diagnosis, often confuses the picture and may render the future diagnosis more difficult.

However, a firm diagnosis can usually be made, and a sensible course of treatment can be planned, but even then results are often better when patients understand their disease and the reasons behind their treatment. The cause and nature of their disease should be explained carefully, in language they can understand, and they must be told what can realistically be expected of their treatment. False optimism or undue pessimism, by patients or doctors, leads only to an unsound relationship. Too often patients become discontented, not because they do not know the correct diagnosis but because they have not been told enough about its cause or prognosis. Even worse, they may have little idea of how to use their treatment and what to expect of it; poor compliance often follows poor instruction. If the treatment is complex, instruction sheets are helpful; they reinforce the spoken word and answer unasked questions.

The principal steps in diagnosis and management are:

- history;
- examination;
- investigations;
- diagnosis;
- explanation of the condition, its cause and prognosis;
- choice of treatment and instructions about it;
- discussion of expectations; and
- follow-up, if necessary.

### Therapeutic options

Some of the treatments used in dermatology are listed in Table 23.1.

<table>
<thead>
<tr>
<th>Therapeutic options in dermatology.</th>
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<tbody>
<tr>
<td>Drugs</td>
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<tr>
<td>Physical</td>
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</table>
Topical vs. systemic therapy

The great advantage of topical therapy is that the drugs are delivered directly to where they are needed, at an optimum concentration for the target organ. Systemic side-effects from absorption are less than those expected from the same drug given systemically: with topical treatment, vital organs such as the marrow, liver and kidneys are exposed to lower drug concentrations than is the skin. However, topical treatment is often messy, time-consuming and incomplete, and takes time to apply, whereas systemic treatment is clean and quick and its effect is uniform over the entire skin surface. Cost must also be considered.

Some drugs can only be used topically (e.g. gamma benzene hexachloride for scabies and mupirocin for bacterial infections), while others only work systemically (e.g. dapsone for dermatitis herpetiformis and griseofulvin for fungal infections).

When a choice exists, and both possibilities are equally effective, then local treatment is usually to be preferred. Most cases of mild pityriasis versicolor, for example, respond to topical antifungals alone so systemic itraconazole is not the first treatment of choice.

Topical treatment

Percutaneous absorption

A drug used on the skin must be dissolved or suspended in a vehicle (base). The choice of the drug and of the vehicle are both important and depend on the diagnosis and the state of the skin. For a drug to be effective topically, it must pass the barrier to diffusion presented by the horny layer (Chapter 2). This requires the drug to be transferred from its vehicle to the horny layer, from which it will diffuse through the epidermis into the papillary dermis. Passage through the horny layer is the rate-limiting step.

The transfer of a drug from its vehicle to the horny layer depends on its relative solubility in each (measured as the ‘partition coefficient’). Movement across the horny layer depends both upon the concentration gradient and on restricting forces (its ‘diffusion constant’). In general, non-polar substances penetrate more rapidly than polar ones. A rise in skin temperature and in hydration, both achieved by covering a treated area with polyethylene occlusion, encourages penetration.

Some areas of skin present less of a barrier than do others. Two extreme examples are palmar skin, with its impermeable thick horny layer, and scrotal skin, which is thin and highly permeable. The skin of the face is more permeable than the skin of the body. Body fold skin is more permeable than nearby unoccluded skin. In humans, absorption through the hair follicles and sweat ducts is of little significance and the amount of hair on the treated site is no guide to its permeability.

In many skin diseases, the horny layer becomes abnormal and loses some of its barrier function. The abnormal nucleated (parakeratotic) horny layers of psoriasis and chronic eczema, although thicker than normal, have lost much of their protective qualities. Water loss is increased and therapeutic agents penetrate more readily. Similarly, breakdown of the horny layer by chemicals (e.g. soaps and detergents) and by physical injury will allow drugs to penetrate more easily.

In summary, the penetration of a drug through the skin depends on the following factors:

• its concentration;
• the base;
• its partition coefficient;
• its diffusion constant;
• the thickness of the horny layer;
• the state, including hydration, of the horny layer; and
• temperature.

Active ingredients

These include corticosteroids, tar, dithranol, antibiotics, antifungal and antiviral agents, benzoyl peroxide, retinoic acid and many others (Formulary 1, p. 328). The choice depends on the action required, and prescribers should know how each works. As topical steroids are the mainstay of much local dermatological therapy, their pharmacology is summarized in Table 23.2.

Vehicles (bases)

Most vehicles are a mixture of powders, water and greases (usually obtained from petroleum). Figure 23.3 shows that blending these bases together produces preparations that retain the characteristics of each of their components.
**Active constituents**
Include hydrocortisone and synthetic halogenated derivatives
Halogenation increases activity

**Bases**
Available as solutions, lotions, creams, ointments, sprays, mousses and tapes

**Penetration**
Readily penetrate via the horny layer and appendages
Form a reservoir in the horny layer
Polyethylene occlusion and high concentrations increase penetration

**Metabolism**
Some minor metabolism in epidermis and dermis (e.g. hydrocortisone converts to cortisone and other metabolites)
Leave skin via dermal vascular plexus and enter general metabolic pool of steroids
Further metabolism in liver

**Excretion**
As sulphate esters and glucuronides

**Actions**
Anti-inflammatory
1. Vasoconstrict
2. Decrease permeability of dermal vessels
3. Decrease phagocytic migration and activity
4. Decrease fibrin formation
5. Decrease kinin formation
6. Inhibit phospholipase A₂ activity and decrease products of arachidonic acid metabolism
7. Depress fibroblastic activity
8. Stabilize lysosomal membranes
Immunosuppressive
Antigen–antibody interaction unaffected but inflammatory consequences lessened by above mechanisms and by inhibiting cytokines (e.g. IFN-γ, GM-CSF, IL-1,2,3 and TNF-α)
Lympholytic
Decrease epidermal proliferation

**Side-effects**
1. Thinning of epidermis
2. Thinning of dermis
3. Telangiectasia and striae (caused by 1 and 2; Figs 23.1 and 23.2)
4. Bruising (caused by 2 and vessel wall fragility)
5. Hirsutism
6. Folliculitis and acneiform eruptions
7. May worsen or disguise infections (bacterial, viral and fungal)
8. Systemic absorption (rare but may be important in infants, when applied in large quantities under polyethylene pants)
9. Tachyphylaxis—lessening of clinical effect with the same preparation
10. Rebound—worsening, sometimes dramatic on withdrawing treatment

**Uses**
Eczema, psoriasis in some instances (facial, flexural, and palms/soles)
Many non-infective, inflammatory dermatoses

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GM-CSF, granulocyte macrophage colony-stimulating factor; INF-γ, γ-interferon; IL, interleukin; TNF, tumour necrosis factor.

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**Table 23.2** The pharmacology of topical steroid applications.
A vehicle should maximize the delivery of topical drugs but may also have useful properties in its own right. Used carelessly, vehicles may even do harm. Suggested indications are shown in Table 23.3. The choice of vehicle depends upon the action desired, availability, messiness, ease of application and cost.

**Individual vehicles**

Dusting powders are used in the folds to lessen friction between opposing surfaces. They may repel water (e.g. talc) or absorb it (e.g. starch); zinc oxide powder has an absorptive power midway between these extremes. Powders ought not be used in moist areas where they tend to cake and abrade.

Watery lotions evaporate and cool inflamed areas. This effect is hastened by adding an alcohol, but glycerol or arachis oil slow evaporation and retain skin moisture. Substances that precipitate protein (astringents; e.g. silver nitrate) lessen exudation.

Shake lotions are watery lotions to which powder has been added so that the area for evaporation is increased. These lotions dry wet weeping skin. When water has evaporated from the skin, the powder particles clump together and may become abrasive. This is less likely if an oil such as glycerol has been added.

Creams are used for their cooling, moisturizing and emollient effects. They are either oil-in-water emulsions [e.g. aqueous cream (UK), acid mantle cream (USA)] or water-in-oil emulsions [e.g. oily cream (UK), cold
use them all, and risk confusion, doctors should limit their choice to one or two from each category. Table 23.3 summarizes the properties and uses of some common preparations.

**Preservatives**

Water-in-oil emulsions, such as ointments, require no preservatives. However, many creams are oil-in-water emulsions that permit contaminating organisms to spread in a continuous watery phase. These preparations therefore, as well as lotions and gels, require the incorporation of preservatives. Those in common use include the parahydroxybenzoic acid esters (parabens), chlorocresol, sorbic acid and propylene glycol. Some puzzling reactions to topical preparations are based on allergy to the preservatives they contain.

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**Table 23.3 Vehicles and their properties.**

<table>
<thead>
<tr>
<th>Base</th>
<th>Used on</th>
<th>Effect</th>
<th>Points of note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dusting powders</td>
<td>Flexures (may be slightly moist)</td>
<td>Lessen friction</td>
<td>If too wet clump and irritate</td>
</tr>
<tr>
<td>Alcohol-based</td>
<td>Scalp</td>
<td>Clean vehicle for steroid application</td>
<td>Cosmetically elegant, do not gum up hair</td>
</tr>
<tr>
<td>applications</td>
<td></td>
<td></td>
<td>May sting raw areas</td>
</tr>
<tr>
<td>(tinctures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watery and shake</td>
<td>Acutely inflamed skin (wet and oozing)</td>
<td>Drying, soothing and cooling</td>
<td>Tedious to apply</td>
</tr>
<tr>
<td>lotions</td>
<td></td>
<td></td>
<td>Frequent changes (lessened by polyethylene occlusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Powder in shake lotions may clump</td>
</tr>
<tr>
<td>Creams</td>
<td>Both moist and dry skin</td>
<td>Cooling, emollient and moisturizing</td>
<td>Short shelf life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fungal and bacterial growth in base</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivities to preservatives and emulsifying agents</td>
</tr>
<tr>
<td>Ointments</td>
<td>Dry and scaly skin</td>
<td>Occlusive and emollient</td>
<td>Messy to apply, soil clothing</td>
</tr>
<tr>
<td>Pastes</td>
<td>Dry, lichenified and scaly skin</td>
<td>Protective and emollient</td>
<td>Messy and tedious to apply (linen or calico needed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Most protective if applied properly</td>
</tr>
<tr>
<td>Sprays</td>
<td>Weeping acutely inflamed skin</td>
<td>Drying, non-occlusive</td>
<td>Vehicle evaporates rapidly</td>
</tr>
<tr>
<td></td>
<td>Scalp</td>
<td></td>
<td>No need to touch skin to treat it</td>
</tr>
<tr>
<td>Gels</td>
<td>Face and scalp</td>
<td>Vehicle for steroids, salicylic acid and tretinoin</td>
<td>May sting when applied to inflamed skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can be covered by make-up</td>
</tr>
<tr>
<td>Mousse</td>
<td>Scalp</td>
<td>Clean vehicle for steroid application</td>
<td>Doesn’t matt the hair</td>
</tr>
</tbody>
</table>

cream (USA)]. Emulsifying agents are added to increase the surface area of the dispersed phase and that of any therapeutic agent in it.

Ointments are used for their occlusive and emollient properties. They allow the skin to remain supple by preventing the evaporation of water from the horny layer. There are three main types:

1. those that are water-soluble (macrogols, polyethylene glycols);
2. those that emulsify with water; and
3. those that repel water (mineral oils, and animal and vegetable fats).

Pastes are used for their protective and emollient properties and usually are made of powder added to a mineral oil or grease. The powder lessens the oil’s occlusive effect.

Variations on these themes have led to the numerous topical preparations available today. Rather than
Methods of application

Ointments and creams are usually applied sparingly twice daily, but the frequency of their application will depend on many factors including the nature, severity and duration of the rash, the sites involved, convenience, the preparation (some new local steroids need only be applied once daily; Formulary 1, p. 332) and, most important, on common sense. In extensive eruptions, a tubular gauze cover keeps clothes clean and hampers scratching (see Fig. 7.19).

Three techniques of application are more specialized: immersion therapy by bathing, wet dressings (compresses) and occlusive therapy.

Bathing

Once-daily bathing helps to remove crusts, scales and medications. After soaking for about 10 min, the skin should be rubbed gently with a sponge, flannel or soft cloth; cleaning may be made easier by soaps, oils or colloidal oatmeal.

Medicated baths are occasionally helpful, the most common ingredients added to the bath water being bath oils, antiseptics and solutions of coal tar.

After cleaning, the most important function of a bath is hydration. The skin absorbs water and this can be held in the skin for some time if an occlusive ointment is applied after bathing.

Older patients may need help to get into a bath and should be warned about falling if the bath contains an oil or another slippery substance.

Wet dressings (compresses)

These are used to clean the skin or to deliver a topical medication. They are especially helpful for weeping, crusting and purulent conditions such as eczema, and are described more fully on p. 75. Five or six layers of soft cloth (e.g. cotton gauze) are soaked in the solution to be used; this may be tap water, saline, an astringent or antiseptic solution, and the compress is then applied to the skin. Open dressings allow the water to evaporate and the skin to cool. They should be changed frequently, e.g. every 15 min for 1 h.

Closed dressings are covered with a plastic (usually polyethylene) sheet; they do not dry out so quickly and are usually changed twice daily. They are especially helpful for debriding adherent crusts and for draining exudative and purulent ulcers.

Occlusive therapy

Sometimes steroid-sensitive dermatoses will respond to a steroid only when it is applied under a plastic sheet to encourage penetration. This technique is best reserved for the short-term treatment of stubborn localized rashes. The drawback of this treatment is that the side-effects of topical steroid treatment (Table 23.2) are highly likely to occur. The most important is systemic absorption if a large surface area of skin, relative to body weight, is treated (e.g. when steroids are applied under the polyethylene pants of infants).

Monitoring local treatment

One common fault is to underestimate the amount required. The guidelines given in Table 23.4 and Fig. 23.4 are based on twice daily applications. Lotions go further than creams, which go further than ointments and pastes.

Pump dispensers have recently become available for some topical steroids which allow measured amounts to be applied. Alternatively, ‘fingertip units’ (Fig. 23.5) can increase the accuracy of prescribing. As a guide,
some drugs act specifically, others non-specifically. For example, antihistamines (H1 blockers) act specifically in urticaria, and non-specifically, by a sedative effect, on the most common skin symptom—itch.

Systemic disease coexists with skin disease in several ways (Chapter 19). Sometimes a systemic disease such as systemic lupus erythematosus may cause a rash; at other times, a skin disease causes a systemic upset. Examples of this are the depression that occurs in some patients affected with severe rashes, and high-output cardiac failure, which may occur in exfoliative dermatitis from the shunting of blood through the skin. A systemic upset caused by skin disease can be treated with drugs designed for such problems while the skin is being treated in other ways.

**Systemic therapy**

Systemic treatment is needed if a skin condition is associated with systemic disease, or if the medicament of choice is inactive topically (e.g. griseofulvin). The principles of systemic therapy in dermatology are no different from those in other branches of medicine:

**Further reading**


The skin can be treated in many ways, including surgery, freezing, burning, ultraviolet radiation and lasers. Some broad principles will be discussed here.

**Surgery**

As our population ages, and becomes more concerned about appearances, requests for skin surgery are becoming more common. The distinction between traditional dermatological surgery and cosmetic surgery is blurring. There are few over the age of 50 years who do not have a benign tumour (Chapter 18) that they consider unsightly and wish to have removed. There are also many who are unhappy with a skin damaged by cumulative sun exposure (see p. 239), or concerned about medically trivial abnormalities on their face. To term the treatment of all these as ‘cosmetic’ seems harsh. Health care systems cannot cover the cost of treating all such problems but family doctors and dermatologists should be able to discuss with their patients any recent developments in phototherapy, laser treatment and specialized surgery that might help them. For example, doctors should be able to explain that diode lasers can remove unwanted hair permanently and without visible scarring, and the pros and cons of such treatment as well as supplying the names of specialists expert in it.

**Skin biopsy**

The indications for biopsy, and the techniques employed, are described in Chapter 3.

**Excision**

Excision under local anaesthetic, using an aseptic technique, is a common way of removing small tumours (Figs 24.1 and 24.2). First, the lesion must be examined carefully and important underlying structures (e.g. the temporal artery) noted. If possible, the incision should run along the line of a skin crease, especially on the face. If necessary, charts or pictures of standard skin creases should be consulted.
Shave excision

Many small lesions are removed by shaving them off at their bases with a scalpel under local anaesthesia. This procedure is suitable only for exophytic tumours that are believed to be benign. Some cells at the base may be left and these, in the case of malignant tumours, would lead to recurrence.

Saucerization excision

This modified shave excision extends into the subcutaneous fat. It is used to remove certain small skin cancers and worrying melanocytic naevi. It leaves more scarring than a shave excision but the technique provides tissue that allows the dermatopathologist to determine if a tumour is invading and to measure...
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for sclerosing basal cell carcinomas, invasive lesions larger than 1–2 cm, rapidly growing tumours or for those with micronodular features on histology.

**Microscopically controlled excision (Mohs’ surgery)**

This form of surgery for malignant skin tumours is time-consuming and expensive, but the probability of cure is greater than with excision or curettage. First, the tumour is removed with a narrow margin. The excised specimen is then marked at the edges, mapped and, after rapid histological processing, is immediately examined in horizontal and vertical section. If the tumour extends to any margin, further tissue is removed from the appropriate place, based on the markings and mappings, and again checked histologically. This process is repeated until clearance has been proved histologically at all margins. The resulting wound can then be closed directly, covered with a split skin graft or allowed to heal by secondary intention.

Mohs’ surgery is useful to treat:
- a basal cell carcinoma with a poorly defined edge;
- a sclerosing basal cell carcinoma (can suggest an enlarging scar clinically);
- a recurrent basal cell carcinoma;
- a basal cell carcinoma lying where excessive margins of skin cannot be sacrificed to achieve complete removal of the tumour (e.g. one near the eye);
- basal cell carcinomas in areas with a high incidence of recurrence such as the nose, glabella or nasolabial folds;
- some squamous cell carcinomas; and
- occasional malignant tumours other than basal and squamous cell carcinomas.

**Flaps and grafts**

These can be used to reconstruct a defect left by the wide excision of a tumour, or when a tumour is removed at a difficult site, e.g. the eyelid or tip of the nose (see Further reading at the end of this chapter as the techniques are beyond the scope of this book).

**Electrosurgery**

This is often combined with curettage, under local anaesthesia, to treat skin tumours. The main types are shown in Fig. 24.7.
freeze–thaw cycles kill tissue more effectively than one but are usually unnecessary for warts and some keratoses (Fig. 24.9). Patients should be warned to expect pain and possible blistering after treatment. Care should be taken when treating warts on fingers as digital nerve damage can occur after overenthusiastic freezing. Standard freeze–thaw times have been established for superficial tumours but temperature probes in and around deep tumours are needed to gauge the degree of freezing for their effective treatment. A crust, including the necrotic tumour, should slough off after about 2 weeks. Melanocytes (p. 242) are very sensitive to cold injury; hypopigmentation at a treated site is common and may be permanent.

**Cryotherapy**

Liquid nitrogen (−196°C) is now used more often than carbon dioxide snow (‘dry ice’, −79°C). It is effective for viral warts, seborrhoeic keratoses, actinic keratoses and some superficial skin tumours (e.g. intraepidermal carcinoma and lentigo maligna). It is applied either on a cotton bud or with a special spray gun (Fig. 24.8). The lesion is frozen until it turns white, with a 1–2 mm halo of freezing around. Two

**Radiotherapy**

Superficial radiation therapy (50–100 kV) can be used to treat biopsy-proven skin cancers in those over
Photodynamic therapy

Photodynamic therapy (PDT) is a new form of phototherapy used for skin cancers and precancers such as superficial basal cell carcinoma less than 2 mm thick (p. 266), intraepidermal carcinoma (p. 325), erythroplasia of Queyrat (p. 188) and actinic keratoses (p. 263). Selective tumour destruction is achieved by incorporating the photosensitizer in the target (malignant) tissue and then activating it with either a laser or non-laser light source. A promising combination is the naturally occurring porphyrin precursor, aminolaevulinic acid (ALA) and irradiation with a red light. The water-soluble ALA (20% in Unguentum M) is applied topically, under occlusion, to the tumour. After 4 h or so, when the ALA has been selectively absorbed by the tumour (Fig. 24.12), the area is exposed to the light for 15–60 min. The activated ALA converts molecular oxygen to cytotoxic singlet oxygen and free radicals, which in turn cause

Phototherapy

Ultraviolet radiation (UVR) helps some conditions (e.g. psoriasis, atopic dermatitis, nummular eczema, parapsoriasis, pityriasis lichenoides, pityriasis rosea, acne and cutaneous T-cell lymphoma; Table 16.4). For psoriasis, UVB (p. 58) may be given up to three times weekly, for 3–8 weeks, on its own or com-
ischaemic necrosis of the tumour by damaging cell membranes, especially those in the walls of blood vessels. PDT is carried out in an outpatient setting and its potential advantages over standard treatments include:
• non-invasiveness;
• ability to treat many lesions at once;
• rarely causes ulceration and leads to a good cosmetic result;
• good patient acceptability; and
• useful for treating tumours on sites that present surgical difficulty, e.g. the taut skin of the finger (Fig. 24.13).

### Laser therapy

Lasers (acronym for light amplification by the stimulated emission of radiation) are high-intensity coherent light sources of a specific wavelength. The photons are absorbed by a target chromophore (e.g. a tattoo pigment, melanin in hair, oxyhaemoglobin in blood vessels) and, depending on the energy, duration of the pulse of emission and the thermal relaxation time, cause local, sometimes microscopic, tissue destruction. Lasers are now being used to treat many skin conditions. A typical example is the treatment of vascular lesions, where the laser is used to coagulate small vessels and capillaries. This produces a localized thermal effect that destroys the blood vessels and results in the resolution of the lesion. The laser is also used for the treatment of tattoos, where the laser energy is absorbed by the tattoo pigment and causes localized heating of the tissue, leading to the destruction of the tattoo pigment and the eventual fading of the tattoo. The laser is also used for the treatment of skin disorders, such as acne, where the laser energy is absorbed by the oil in the skin and causes localized heating of the skin, leading to the destruction of the bacteria and the resolution of the acne. The laser is also used for the treatment of scalp hair growth, where the laser energy is absorbed by the hair follicles and causes localized heating of the follicles, leading to the destruction of the hair follicles and the reduction of hair growth. The laser is also used for the treatment of skin diseases, such as psoriasis, where the laser energy is absorbed by the skin and causes localized heating of the skin, leading to the destruction of the skin cells and the resolution of the psoriasis. The laser is also used for the treatment of skin warts, where the laser energy is absorbed by the wart and causes localized heating of the wart, leading to the destruction of the wart. The laser is also used for the treatment of skin cancers, where the laser energy is absorbed by the cancer and causes localized heating of the cancer, leading to the destruction of the cancer.
lesions including capillary haemangiomas, tattoos, epidermal naevi, pigmented lesions, seborrhoeic keratoses, warts and tumours.

Since 1960, when T.H. Maiman won the Nobel Prize for inventing the first laser, technology has advanced rapidly and many types of laser are now available for clinical use. Most treatments can be carried out under local anaesthetic and as an outpatient. Port-wine stains can be treated successfully in children as well as in adults, using the flashlamp pulsed dye laser emitting light at 585 nm. Most tattoos can be removed by treatment with a Q-switched ruby laser (694 nm), a flashlamp pumped pulsed dye laser (510 nm) or an alexandrite laser (760 nm). Scarring should not be a problem. Benign but unsightly pigmented lesions such as café au lait marks, melasma, the naevus of Ota and senile lentigines can be greatly improved by treatment with the flashlamp pumped pulsed dye laser (510 nm) and the Q-switched neodymium: yttrium aluminium garnet (Nd:YAG) laser (532 nm). Unwanted hair can be permanently removed with a pulsed diode laser (800 nm) or with a Q-switched Nd:YAG laser emitting light at 1064 nm.

Rhinophyma, sebaceous gland hyperplasia, seborrhoeic keratoses, syringomas and many of the signs of chronic photodamage (e.g. rhytides, actinic cheilitis, actinic keratoses) can be helped by cutaneous resurfacing using CO₂ lasers emitting a wavelength of 10 600 nm (infrared) or a Q-switched erbium (Er): YAG laser emitting pulsed waves of 2940 nm in the near infrared, which is absorbed by water 10 times more efficiently than the pulsed CO₂ laser beam (Fig. 24.14). Good postoperative care is important, as the patient is left with what is essentially a partial thickness burn which heals by re-epithelialization from the cutaneous appendages. After profuse exudation for 24–48 h the treated area heals, usually in 5–10 days. Absolute contraindications for laser resurfacing include the use of isotretinoin within the previous year, concurrent bacterial or viral infection and any hint of ectropion. Dark skin (skin types V and VI; p. 233) should be treated with special care as pigmentary side-effects are common. Cutaneous laser resurfacing is more effective on the face than on the neck and extremities.

Laser treatments should be carried out only by fully trained specialists.

Further reading


Our selection has been determined by personal preferences and we accept that we have left out many effective remedies. However, the preparations listed here are those that we use most often. As a result some appear only in the UK column but not in the USA one, and vice versa. To conform with current prescribing recommendations whenever possible we have listed these products under their active ingredients, with their proprietary names in brackets.

<table>
<thead>
<tr>
<th>Type of preparation and general comments</th>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emollients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>These are used to make dry scaly skin smoother. Most are best applied after a shower or bath</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soft white paraffin BP</td>
<td>Vanacream—devoid of fragrances and many sensitizers</td>
</tr>
<tr>
<td></td>
<td>Emulsifying ointment BP</td>
<td>Aquaphor—a hydrophilic petrolatum</td>
</tr>
<tr>
<td></td>
<td>Aqueous cream BP—can be used as a soap substitute</td>
<td>Plastibase—a hydrophilic polyglycol</td>
</tr>
<tr>
<td></td>
<td>Diprobase cream and ointment</td>
<td>Eucerin—hydrophilic petrolatum containing water</td>
</tr>
<tr>
<td></td>
<td>E45 range</td>
<td>Oilatum range</td>
</tr>
<tr>
<td></td>
<td>Oilatum range</td>
<td>Unguentum M—a useful diluent: contains propylene glycol and sorbic acid, which may sensitize</td>
</tr>
<tr>
<td></td>
<td>Neutrogena dermatological cream</td>
<td>Neutrogena dermatological cream</td>
</tr>
<tr>
<td></td>
<td>Aquadrate cream—contains urea</td>
<td>Curel</td>
</tr>
<tr>
<td></td>
<td>Calmurid cream—contains urea</td>
<td>Moisturel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lubraderm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carmol range—contains urea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tricream—ceramide-dominant barrier repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bath additives/shower gels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>These are a useful way of ensuring application to the whole skin. Most contain emollients which help with dry itchy skin. Others contain tar (see section on psoriasis) or antibacterials</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balneum range</td>
<td>Oatmeal range</td>
</tr>
<tr>
<td></td>
<td>Emulsiderm—contains benzalkonium chloride</td>
<td>Mineral oil bath emulsion (Keri Moisture Rich Shower and Bath Oil)</td>
</tr>
<tr>
<td></td>
<td>Oatatum range</td>
<td>Colloidal oatmeal (Aveeno Moisturizing Formula Bath)</td>
</tr>
<tr>
<td></td>
<td>Aveeno range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ster-Zac bath concentrate—contains antibacterial triclosan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydromol bath emollient</td>
<td></td>
</tr>
<tr>
<td>Type of preparation and general comments</td>
<td>UK preparation</td>
<td>USA</td>
</tr>
<tr>
<td>------------------------------------------</td>
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<td>-----</td>
</tr>
<tr>
<td><strong>Shampoos</strong></td>
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</tr>
</tbody>
</table>
| All contain detergents which help to remove debris and scales; some have added ingredients to combat psoriasis, seborrhoeic eczema and bacterial infections. Most work best if their lather is left on the scalp for 5 min before being rinsed off | Containing tar  
Alphosyl 2 in 1  
Polytar range  
T-Gel  
Capasal—also contains salicylic acid | Containing tar  
Pentax shampoo  
Sebutone shampoo  
Denorex shampoo—tingles on scalp  
T-Gel  
Polytar range |
| **Others**                                |                |     |
| Betadine—contains antibacterial povidone iodine | Betadine (Head and Shoulders, Zincon)  
Ketoconazole (Nizoral shampoo) useful for seborrhoeic dermatitis and pityriasis versicolor  
Zinc pyrithione (Head and Shoulders, Zincon)  
Contains salicylic and sulfur (Meted, Sebulex)  
Fluocinonide (Caprex shampoo) |  |
| Ceanel concentrate—contains cetrimide, undecenoic acid |  |  |
| Selsun—contains selenium sulphide and can be used to treat pityriasis versicolor (p. 221) |  |  |
| Nizoral—contains ketoconazole and is useful for seborrhoeic dermatitis and pityriasis versicolor |  |  |
| Meted—contains salicylic acid and sulphur |  |  |
| **Cleansing agents**                      |                |     |
| These are used to remove debris and to combat infection. Some are astringents which precipitate protein and in doing so help to seal the moist surface of a weeping eczema or a stasis ulcer | Solution of sodium chloride 0.9% (Normasol)—used to clean wounds and ulcers  
Potassium permanganate (Permitabs—one tablet in 4 L water makes a 0.01% solution)—will stain clothing and skin  
Aluminium acetate lotion—use at 0.65% in water—is mildly astringent and used as wet dressing  
Silver nitrate—use at 0.5% in water—is astringent, stains skin brown  
Chlorhexidine/cetrimide (Hibicet Hospital Concentrate—dilute to 1 in 100) | Chlorhexidine 5% (Hibiclens) concentrate—use diluted to 1 in 100 (a 0.05% solution of chlorhexidine in water for skin disinfection)  
Cetaphil gentle skin cleanser (lipid-free)  
Benzalkonium chloride (Ionax line)  
Triclosan (Dial, Lever 2000)—deodorant, antibacterial  
Sulfacetamide/Sulfur (Plexon)—cleanser for rosacea |
| **Barrier preparations**                  |                |     |
| These are used to protect the skin from irritants and are of value in the napkin (diaper) area and around stomas. Many contain the silicone, dimethicone. The choice of barrier creams for use at work depends upon individual circumstances: recommendations are not given here | Zinc and castor oil ointment BP  
Dimethicone and benzalkonium chloride (Conotrane)  
Dimethicone and cetrimide (Siopel)  
Dimethicone, calamine and zinc oxide (Vasogen) | Zinc oxide ointment  
Kerodex 51 (water-miscible)  
Kerodex 71 cream (water-repellant)  
Bentoquatum (Ivy Block Lotion) protective against toxicodendron (poison ivy allergy)  
Dermaguard spray  
Flexible collodion (film) |
### Type of preparation and general comments

<table>
<thead>
<tr>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>None in BNF but some preparations available without prescription from chemists/cosmetic counters</td>
<td>Hydroquinone 2–4% (Melanex topical solution—contains 3% hydroquinone, Solaquin forte—contains 4% hydroquinone and sunscreen, Glyquin—contains 10% glycolic acid and 4% hydroquinone)</td>
</tr>
<tr>
<td>Boots Covering Cream, Covermark range, Dermablend range, Keromask range</td>
<td>Covermark range of products, Dermablend, Powder Palette (Physician’s Formula—Pierre Fabre) in green for correcting red blush of rosacea</td>
</tr>
<tr>
<td>Cinnamate and oxybenzone (RoC Total Sunblock cream), Uvistat range, Titanium dioxide (Sun E45 range)</td>
<td>Cinnamates, benzophenones, and salicylates: Coppertone waterproof lines, Neutrogena sunblock lines, Presun active clear gel, Lubraderm daily UV lotion</td>
</tr>
<tr>
<td>Cinnamate, oxybenzene and titanium dioxide (Sunsense Ultra)</td>
<td>Avobenzone 3%, Homosalate 12%, Octy methoxycinnamate 7.5%, Octocrylene 1.5%, Oxybenzone 6% (Solbar PF)</td>
</tr>
<tr>
<td>Calamine lotion BP, Oily Calamine lotion BP—contains arachis oil</td>
<td>Zinc oxide ointment</td>
</tr>
<tr>
<td>Zinc oxide, lanolin, t alc and vitamins A and D (Desitin ointment)</td>
<td>Zinc Oxide 8%, Titanium dioxide 3% (Vanicream Sunscreen)</td>
</tr>
<tr>
<td>Dimethicone (Diaper Guard Ointment)</td>
<td></td>
</tr>
<tr>
<td>Anusol (zinc oxide plus pramoxine)</td>
<td></td>
</tr>
<tr>
<td>Bag Balm (contains 8-hydroxyquinoline sulfate)</td>
<td></td>
</tr>
<tr>
<td>Hydroquinone 2–4% (Melanex topical solution—contains 3% hydroquinone, Solaquin forte—contains 4% hydroquinone and sunscreen, Glyquin—contains 10% glycolic acid and 4% hydroquinone)</td>
<td></td>
</tr>
<tr>
<td>Hydroquinone (4%), tretinoin (0.05%) and fluocinonide (0.01%) (Tri-Luma)</td>
<td></td>
</tr>
<tr>
<td>Monobenzene/monobenzyl ether of hydroquinone (Benaquin) (Caution: permanent depigmentation)</td>
<td></td>
</tr>
</tbody>
</table>

### Depigmenting agents
These contain hydroquinone. The use of agents containing monobenzone causes permanent complete depigmentation.  

### Camouflaging preparations
Blemishes which cannot be removed can often be made less obvious by covering them. Expert cosmetic advice may be needed to obtain the best colour match.

### Sunscreens and sunblocks
These help the light-sensitive but are not a substitute for sun avoidance and sensible protective clothing. The sun protection factor (SPF) is a measure of their effectiveness against UVB more than UVA, but those recommended here block UVA also.

Allergic contact dermatitis from the sunscreen ingredients may be missed and the rash put down to a deterioration of the original photosensitivity.

### Antipruritics
Remember that these are of limited value: try to make a firm diagnosis which will lead to an effective line of treatment.
### TOPICAL TREATMENTS

<table>
<thead>
<tr>
<th>Type of preparation and general comments</th>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiperspirants</strong></td>
<td>Menthol (0.5%) or phenol (1.0%) in aqueous cream</td>
<td>Menthol and camphor (Sarna lotion) contains menthol and camphor</td>
</tr>
<tr>
<td></td>
<td>Crotamiton cream and lotion (Eurax)—also used to treat scabies</td>
<td>Menthol, phenol and zinc oxide (Shamberg’s lotion)</td>
</tr>
<tr>
<td></td>
<td>Doxepin (Xepin cream)</td>
<td>Doxepin (Zonalon cream)</td>
</tr>
<tr>
<td></td>
<td>Aluminium chloride hexahydrate 20% (Anhydrol Forte solution or Driclor solution)</td>
<td>Aluminum chloride 20% (Drysol)</td>
</tr>
<tr>
<td></td>
<td>Aluminum chloride hexahydrate 20% (Anhydrol Forte solution or Driclor solution)</td>
<td>12.5% (CertainDry Roll-On), 6.25% (Xerac-AC)</td>
</tr>
<tr>
<td></td>
<td>Formaldehyde 10% solution (Lazerformaldehyde)—caution: may sensitize</td>
<td>Formaldehyde 10% solution (Lazerformaldehyde)—caution: may sensitize</td>
</tr>
<tr>
<td><strong>Keratolytics</strong></td>
<td>Salicylic acid, 2–4% in emulsifying ointment or soft white paraffin</td>
<td>Urea preparations (see Emollients above)</td>
</tr>
<tr>
<td></td>
<td>Urea preparations (see Emollients above)</td>
<td>Urea preparations (see Emollients above)</td>
</tr>
<tr>
<td></td>
<td>Propylene glycol, 20% in aqueous cream</td>
<td>Propylene glycol (Epilyt)</td>
</tr>
<tr>
<td><strong>Depilatories</strong></td>
<td>None in BNF but freely available over-the-counter</td>
<td>Sulfides (Magic Shaving Powder)</td>
</tr>
<tr>
<td></td>
<td>None in BNF but freely available over-the-counter</td>
<td>Thioglycollates (Nair line, Neet line)</td>
</tr>
<tr>
<td></td>
<td>None in BNF but freely available over-the-counter</td>
<td>Zip wax, Nair microwave wax—mechanical hair removal</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Mildly potent Hydrocortisone 0.5, 1.0, 2.5% preparations</td>
<td>Mildly potent Hydrocortisone 0.5, 1.0, 2.5% (numerous manufacturers)</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide (Synalar cream 1 in 10)</td>
<td>Desonide (Desowen, Tridesilon)</td>
</tr>
<tr>
<td></td>
<td>Alclometasone dipropionate (Modrasone cream and ointment)</td>
<td>Alclometasone (Aclovate)</td>
</tr>
<tr>
<td><strong>Moderately potent</strong></td>
<td>Betamethasone valerate (Betnovate RD cream and ointment)</td>
<td>Betamethasone valerate (Valisone)</td>
</tr>
<tr>
<td></td>
<td>Clobetasone butyrate cream and ointment (Eumovate)</td>
<td>Fluticasone (Cutivate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone valerate (Westcort)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triamcinolone 0.025%, 0.1% (Kenalog, Aristocort, various manufacturers)</td>
</tr>
</tbody>
</table>

Continued p. 332
reluctant to prescribe more than 200 g of a mildly potent, 50 g of a moderately potent, or 30 g of a potent preparation per week for any adult for more than a month

Most of the preparations listed are available as lotions, creams, oily creams, and ointments; your choice of vehicle will depend upon the condition under treatment (p. 317). Use twice daily except for Cutivate and Elocon, which are just as effective if used once a day

**Steroid combinations**

<table>
<thead>
<tr>
<th>Type of preparation and general comments</th>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent</strong></td>
<td>Betamethasone valerate (Betnovate range including scalp application, Betacap scalp application, Bettamousse scalp application)</td>
<td>Betamethasone dipropionate (Diprosone)</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate (Cutivate cream and ointment)</td>
<td>Diflorasone (Elocon)</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate (Elocon range)</td>
<td>Fluocinonide (Lidex)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 17-butyrate (Locoid range)</td>
<td>Desoximetasone (Topicort 0.025%)</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide (Synalar range)</td>
<td></td>
</tr>
<tr>
<td><strong>Very potent</strong></td>
<td>Clobetasol propionate (Dermovate range)</td>
<td>Clobetasol (Tenovate)</td>
</tr>
<tr>
<td></td>
<td>Halcinonide (Halciderm cream)</td>
<td>Halobetasol (Ultravate)</td>
</tr>
<tr>
<td></td>
<td>Diflucortolone valerate (Nerisone Forte range)</td>
<td>Betamethasone dipropionate in enhanced vehicle (Diprolene)</td>
</tr>
<tr>
<td><strong>Mildly potent</strong></td>
<td>Hydrocortisone and clioquinol (Vioform-hydrocortisone cream and ointment)</td>
<td>Clioquinol and hydrocortisone (1%)</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate and clioquinol (Betnovate-C cream and ointment)</td>
<td>Iodoquinol 1% and hydrocortisone 1% (Vytone cream)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone 17-butyrate with chlorquinaldol (Locoid-C cream and ointment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide with clioquinol (Synalar-C cream and ointment)</td>
<td></td>
</tr>
<tr>
<td><strong>Mildly potent</strong></td>
<td>Hydrocortisone and oxytetracycline (Terra-Cortril ointment)</td>
<td>Polysporin, neomycin, bacitracin, hydrocortisone 1% (Corticosporin)</td>
</tr>
<tr>
<td><strong>Moderately potent and potent</strong></td>
<td>Betamethasone valerate and neomycin (Betnovate-N cream and ointment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide and neomycin (Synalar-N cream and ointment)</td>
<td></td>
</tr>
<tr>
<td><strong>Mildly potent</strong></td>
<td>Hydrocortisone and clotrimazole (Canesten HC cream)</td>
<td>Clotrimazole and betamethasone dipropionate (Lotrisone)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone and miconazole (Daktacort cream and ointment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone and econazole (Econacort)</td>
<td></td>
</tr>
<tr>
<td>Type of preparation and general comments</td>
<td>UK preparation</td>
<td>USA</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-----</td>
</tr>
<tr>
<td>With antibacterials and antifungals</td>
<td>Mildly potent</td>
<td></td>
</tr>
<tr>
<td>With tar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With Calcipotriol</td>
<td>Potent only</td>
<td></td>
</tr>
<tr>
<td>With salicylic acid</td>
<td>Potent only</td>
<td></td>
</tr>
<tr>
<td>Preparations for use in the mouth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### With antibacterials and antifungals

<table>
<thead>
<tr>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mildly potent  Hydrocortisone, chlorhexidine and nystatin (Nystaform HC cream and ointment)</td>
<td>Moderately potent Neomycin, nystatin, triamcinolone 0.1% (Mycolog II)</td>
</tr>
<tr>
<td>Hydrocortisone, oxytetracycline and nystatin (Terra-Cortril Nystatin cream)</td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone, benzalkonium, nystatin and dimeticone (a silicone) (Timodine cream)</td>
<td></td>
</tr>
<tr>
<td>Moderate potent Clobetasone butyrate, oxytetracycline and nystatin (Trimovate cream)</td>
<td></td>
</tr>
<tr>
<td>Very potent Clobetasol propionate, neomycin and nystatin (Dermovate NN cream and ointment)</td>
<td></td>
</tr>
<tr>
<td>With tar Mildly potent only Hydrocortisone, allantoin and coal tar extract (Alphosyl HC cream)</td>
<td>Potent only Betamethasone dipropionate (Dovobet ointment)</td>
</tr>
<tr>
<td>With Calcipotriol Potent only Betamethasone dipropionate (Dovobet ointment)</td>
<td></td>
</tr>
<tr>
<td>With salicylic acid Potent only Betamethasone dipropionate and salicylic acid (Diprosalic ointment—and scalp application)</td>
<td></td>
</tr>
</tbody>
</table>

### Preparations for use in the mouth

<table>
<thead>
<tr>
<th>Useful mouth washes</th>
<th>Cetylpyridinium (Cepacol antiseptic mouthwash)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzydamine solution (Difflam oral rinse)—an analgesic for painful inflammation in the mouth</td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine (Corsodyl mouthwash)</td>
<td>Listerine antiseptic mouthrinse</td>
</tr>
<tr>
<td>Hexetidine solution (Oraldene) an antiseptic gargle</td>
<td>(contains thymol, eucalyptol, methylsalicylate, menthol)</td>
</tr>
<tr>
<td>'All-purpose mouthwash’—different formulations—e.g. compounded as nystatin suspension 100 000 U/ml, 120 ml; diphenhydramine elixir 12.5 mg/5 ml, 480 ml; hydrocortisone powder 240 mg; sodium carboxymethylcellulose 2%, 720 ml</td>
<td></td>
</tr>
<tr>
<td>Type of preparation and general comments</td>
<td>UK preparation</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Topical steroids</strong></td>
<td>Triamcinolone acetonide (Adcortyl in Orabase) a paste that adheres to mucous membranes</td>
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<tr>
<td></td>
<td>Hydrocortisone pellets (Corlan pellets) to be dissolved slowly in mouth near the lesion—usually an aphthous ulcer</td>
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<tr>
<td></td>
<td>Miconazole (Daktarin oral gel)</td>
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<td></td>
<td>Amphotericin (Fungilin lozenges)</td>
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<tr>
<td></td>
<td>Nystatin (Nystan oral suspension)</td>
</tr>
<tr>
<td><strong>For yeast infections</strong></td>
<td>Tacrolimus (Protopic ointment 0.03%, 0.1%)</td>
</tr>
<tr>
<td></td>
<td>Pimecrolimus (Elidel cream 1%)</td>
</tr>
<tr>
<td><strong>Topical immunomodulators</strong></td>
<td>Aluminium acetate ear drops 8%—an effective astringent for the weeping phase: best applied on ribbon gauze</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone with neomycin and polymyxin (Otosporin drops)</td>
</tr>
<tr>
<td></td>
<td>Cotrimazole (Canesten solution)</td>
</tr>
<tr>
<td><strong>Preparations for otitis externa</strong></td>
<td>Mupirocin (Bactroban cream and ointment)</td>
</tr>
<tr>
<td></td>
<td>Fusidic acid (Fucidin ointment, cream or gel)</td>
</tr>
<tr>
<td></td>
<td>Neomycin and gramicidin (Graneodin ointment)</td>
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<tr>
<td></td>
<td>Polymyxin and Bacitracin (Polyfax ointment)</td>
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<tr>
<td>To eliminate nasal carriage of staphylococci</td>
<td>Mupirocin (Bactroban Nasal cream) Chlorhexidine and neomycin (Naseptin cream)</td>
</tr>
<tr>
<td>Type of preparation and general comments</td>
<td>UK preparation</td>
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<td>------------------------------------------</td>
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</tr>
<tr>
<td><strong>Antifungal preparations</strong></td>
<td></td>
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<tr>
<td>In our view imidazole, terbinafine, butenafine and amorolfine creams have now supplanted their messier, more irritant, and less effective rivals (e.g. Whitfield’s ointment). They have the added advantage of combating yeasts as well as dermatophytes. Systemic therapy will be needed for tinea of the scalp, of the nails, and of widespread or chronic skin infections which prove resistant to topical treatment.</td>
<td>Clotrimazole (Canesten cream) Miconazole (Daktarin cream) Terbinafine (Lamisil cream) Amorolfine (Loceryl cream and nail lacquer) Tioconazole (Trosyl nail solution)—applied locally it may increase the success rate of griseofulvin. Used by itself it may also cure or improve some nails</td>
</tr>
<tr>
<td><strong>Antiviral preparations</strong></td>
<td></td>
</tr>
<tr>
<td>These have little part to play in the management of herpes zoster. However, if used early and frequently, they may help with recurrent herpes simplex infections.</td>
<td>Aciclovir cream Idoxuridine in dimethyl sulphoxide (Herpid application)—absorption of dimethyl sulphoxide may cause a garlic-like taste</td>
</tr>
<tr>
<td><strong>Wart treatments</strong></td>
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<tr>
<td><strong>Palmoplantar warts</strong></td>
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<tr>
<td>Salicylic acid and lactic acid (Salactol paint or Salatac and Cuplex gel) Salicylic acid (at 26%, Occlusal solution: at 50%, Verrugon ointment) Glutaraldehyde (Glutarol solution) Formaldehyde (Veracur gel)</td>
<td></td>
</tr>
<tr>
<td><strong>Anogenital warts</strong></td>
<td></td>
</tr>
<tr>
<td>Podophyllin resin (Podophyllin paint compound)—use with care (p. 205) Podophyllotoxin (Condylone solution) Imiquimod (Aldara cream)—an immunomodulator (p. 205)</td>
<td></td>
</tr>
<tr>
<td><strong>Preparations for treatment of scabies</strong></td>
<td></td>
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<tr>
<td>Poor results follow inefficient usage rather than ineffective preparations. We prefer Lyclear or precipitated sulphur in young children, and pregnant and lactating women. Written instructions are helpful (p. 230)</td>
<td>Permethrin (Lyclear Dermal Cream) Benzyl benzoate application (BP) Malathion (Quellada M liquid or Derbac-M liquid) Precipitated sulphur 6% in soft white paraffin Crotamiton (Eurax cream) for use if itching persists after treatment with more effective scabicides</td>
</tr>
<tr>
<td>Type of preparation and general comments</td>
<td>UK preparation</td>
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<td>-----------------------------------------</td>
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</tr>
<tr>
<td><strong>Preparations for treatment of pediculosis</strong></td>
<td>Resistance to lindane has limited its usefulness for scalp lice. Lotions left on for a minimum of 12 h are perhaps more effective, although less convenient than shampoos</td>
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<tr>
<td><strong>Preparations for acne</strong></td>
<td>Active ingredient</td>
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<td></td>
<td>Retinoids</td>
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<td>Antibiotics</td>
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<tr>
<td></td>
<td>Abrasives</td>
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<td></td>
<td>Sulphur</td>
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<td></td>
<td>Azelaic acid and salicylic acid</td>
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<tr>
<td><strong>Preparations for rosacea</strong></td>
<td>Metronidazole (Metrogel or Zyomet gels)</td>
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</tbody>
</table>
### Preparations for psoriasis

#### Vitamin D derivatives
Calcipotriol (calcipotriene, USA) and tacalcitol. Avoid using in patients with disorders of calcium metabolism. May irritate initially

- **UK preparation**: Calcipotriol (Dovonex cream, ointment and scalp solution).
  - Maximum weekly doses: 6–12 years, 50 g; 12–16 years, 75 g; adults, 100 g
  - Tacalcitol (Curatoderm ointment).
  - Maximum daily dose for adults, 10 g. Not recommended for children

- **USA**: Calcipotriene (Dovonex cream, lotion, and ointment)
  - Same as UK

#### Steroids
Routine long-term treatment with potent or very potent steroids is not recommended. For indications (p. 57)

- **Scalp applications**
  - Betamethasone (Betnovate scalp application, Diprosalic scalp lotion—also contains salicylic acid)
  - Fluocinolone (Synalar gel)

- **For use elsewhere**
  - Dithrocream range
  - Micanol range

  - **Tar—steroid combinations are helpful** (See section on topical steroids above)

  - **Dithranol/anthralin**
  - Stains normal skin and clothing. May be irritant, therefore start with low concentration. For 30-minute regimen see p. 58

  - **Tar**
  - These clean refined tar preparations are suitable for home use. Messier, although more effective, formulations exist but are best used in treatment centres

- **Applications**
  - Alphosyl cream Carbo-Dome cream
  - Psoriderm cream

  - **Bath additives**
  - Polytar emollient
  - Psoriderm bath emulsion

  - **Grinstead liquid**

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*Continued p. 338*
<table>
<thead>
<tr>
<th>Type of preparation and general comments</th>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp applications</td>
<td>Alphosyl lotion</td>
<td>Neutrogena T Gel therapeutic conditioner</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Cocos ointment (see Keratolytics)</td>
<td>10% Liquor carbonis detergens in Nivea oil</td>
</tr>
<tr>
<td>Tar–salicylic acid combinations</td>
<td>Pragmatar cream—also contains sulphur</td>
<td>Scalpicin Hypoallergenic Formula</td>
</tr>
<tr>
<td><strong>Preparations for venous ulcers</strong></td>
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<tr>
<td>Regardless of topical applications, venous ulcers will heal only if local oedema is eliminated. Remember that the surrounding skin is easily sensitized. To choose treatment for an individual ulcer (p. 142)</td>
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<tr>
<td><strong>For cleansing</strong></td>
<td>Saline, potassium permanganate (see Cleansing agents above)</td>
<td>Saline, potassium permanganate (see Cleansing agents)</td>
</tr>
<tr>
<td></td>
<td>Hydrogen peroxide solution (3%)</td>
<td>Hydrogen peroxide solution (3%)</td>
</tr>
<tr>
<td><strong>Antibacterial gauze dressings</strong></td>
<td>Chlorhexidine (Bactigras tulle)</td>
<td>Enzymes (Elase Ointment—contains fibrinolysin and desoxyribonuclease; Collagenase Santyl ointment—contains collagenase)</td>
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<tr>
<td></td>
<td>Soframycin (Sofra-tulle)</td>
<td>Silver sulfadiazine (Silvadene cream) Nitrofurazone (Nitrofurazone solution) Mupirocin (Bactroban Ointment)</td>
</tr>
<tr>
<td><strong>Other applications</strong></td>
<td>Silver sulfadiazine—active against <em>Pseudomonas</em> (Flamazine cream)</td>
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<td></td>
<td>Silver nitrate aqueous solution (0.5%)</td>
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<tr>
<td></td>
<td>Cadexomer iodine (Iodosorb powder)</td>
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</tr>
<tr>
<td><strong>Medicated bandages</strong></td>
<td>Zinc paste and calamine (Calaband)</td>
<td></td>
</tr>
<tr>
<td>Beware of allergic contact reactions to parabens preservatives which are in most bandages</td>
<td>Zinc paste and ichthammol (Ichthopaste)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zinc oxide (Viscopaste PB7)</td>
<td></td>
</tr>
<tr>
<td><strong>Other dressings</strong></td>
<td>Hydrocolloid (Granuflex, DuoDERM Extra Thin)</td>
<td>Hydrocolloid (Duoderm)</td>
</tr>
<tr>
<td></td>
<td>Calcium alginate (Kaltostat)</td>
<td>Vapour-permeable film dressing (Opsite, Tegaderm)</td>
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<tr>
<td></td>
<td>Polyurethane foam (Tielle)</td>
<td>Hydrogel (Vigilon) Dextranomer (Debrisan)</td>
</tr>
<tr>
<td></td>
<td>Vapour-permeable film dressing (Opsite)</td>
<td>Calcium alginate</td>
</tr>
<tr>
<td></td>
<td>Activated charcoal with silver (Actisorb silver)</td>
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<td></td>
<td>Dextranomer (Debrisan)</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Efudix cream</td>
<td>Efudex cream 1.5%</td>
</tr>
<tr>
<td>5-Flourouracil</td>
<td></td>
<td>Carac 0.5% (Dermik)—drug incorporated into microsphere</td>
</tr>
</tbody>
</table>
**Type of preparation and general comments**

<table>
<thead>
<tr>
<th></th>
<th>UK preparation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>keratoses is tedious or impossible. For such cases 1–5% cream containing 5-fluorouracil is useful. It should be applied twice daily for 2–3 weeks. Patients should be warned about the inevitable inflammation and soreness which appears after a few days. Lesions on the scalp and face do better than those on the arms and hands</td>
<td>Regaine liquid 2 or 5%—only on private prescription</td>
<td>Rogaine 2% solution</td>
</tr>
<tr>
<td><strong>Minoxidil</strong></td>
<td>May be used as a possible treatment for early male-pattern alopecia. The response is slow, and only a small minority of patients will obtain a dense regrowth even after 12 months. Hair regained will fall out when treatment stops—warn patients about this</td>
<td>Axsain cream (0.075%)</td>
</tr>
<tr>
<td><strong>Capsaicin</strong></td>
<td>A topical analgesic useful for the treatment of post-herpetic neuralgia. Apply up to 3–4 times daily after lesions have healed. May take 2–4 weeks to relieve pain</td>
<td>Effalith ointment</td>
</tr>
<tr>
<td><strong>Lithium succinate</strong></td>
<td>A topical anti-inflammatory used in seborrhoeic dermatitis</td>
<td></td>
</tr>
<tr>
<td><strong>Lidocaine/prilocaine</strong></td>
<td>A local anaesthetic for topical use. Applied on skin as a thick layer of cream under an occlusive dressing or on adult genital mucosa with no occlusive dressing. Read manufacturer’s instructions for times of application</td>
<td>Lidocaine and prilocaine (EMLA cream)</td>
</tr>
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</tbody>
</table>
We list here only preparations we use commonly for our patients with skin disease. The doses given are the usual oral doses for adults. We occasionally use some of these drugs for uses not approved by federal regulatory agencies. We have included some, but not all, of the side effects and interactions; these are more fully covered in the British National Formulary (BNF) (UK) and Physician’s Desk Reference (PDR) (USA). Physicians prescribing these drugs should read about them there, in more detail, and specifically check the dosages before treating their patients. If possible, systemic medication should be avoided in pregnant women.

<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefalexin and Cefuroxime</td>
<td>Gut upsets</td>
<td>Probenecid reduces excretion</td>
<td>Not usually indicated as first-line or blind therapy</td>
</tr>
<tr>
<td>Cephalosporins not inactivated by penicillinase.</td>
<td>Candidiasis</td>
<td></td>
<td>Ten per cent of penicillin allergic patients will react to this</td>
</tr>
<tr>
<td>For Gram-positive and -negative infections resistant to penicillin and erythromycin (Cefalexin 250–500 mg four times daily; Cefuroxine 250 mg twice daily)</td>
<td>Rarely, erythema multiforme or toxic epidermal necrolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Gut upsets</td>
<td>Antacids reduce absorption</td>
<td>Crystalluria if fluid intake is inadequate</td>
</tr>
<tr>
<td>A 4-quinolone used for Gram-negative infections, especially pseudomonas, and Gram-positive infections. First choice for skin infections in the immunosuppressed if the causative organism is not yet known (500 mg twice daily)</td>
<td>Occasionally hepatotoxic and nephrototoxic</td>
<td>Enhances effects of warfarin and theophylline</td>
<td>Care if renal impairment</td>
</tr>
<tr>
<td>Haemolysis in those deficient in glucose-6-phosphate dehydrogenase</td>
<td></td>
<td></td>
<td>Avoid in pregnancy, breast feeding, children and epileptics</td>
</tr>
<tr>
<td>Co-amoxiclav (Augmentin)</td>
<td>Gut upsets</td>
<td>As for other penicillins</td>
<td>Use with care in hepatic or renal failure, pregnancy, and breast feeding</td>
</tr>
<tr>
<td>A broad-spectrum penicillin combined with clavulanic acid: use if organisms resistant to both</td>
<td>Candidiasis</td>
<td></td>
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<tr>
<td>Rashes, especially in infectious mononucleosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Main dermatological uses and usual adult doses</td>
<td>Adverse effects</td>
<td>Interactions</td>
<td>Other remarks</td>
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<tr>
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</tr>
<tr>
<td>Erythromycin and flucloxacillin. Also for Gram-negative folliculitis (375 mg three times daily)</td>
<td>Gut upsets</td>
<td>Increased risk of toxicity if given with theophylline or carbamazepine</td>
<td>Avoid in those allergic to penicillin</td>
</tr>
<tr>
<td>1 Acne vulgaris (250–500 mg twice daily)</td>
<td>Rashes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Gram-positive infections, particularly staphylococcal and streptococcal. Useful with penicillin allergy (250–500 mg four times daily)</td>
<td>Cholestatic hepatitis if treatment prolonged (reversible and most common with estolate salt)</td>
<td>Potentiates effects of warfarin, ergotamine, cyclosporin A, disopyramide, carbamazepine, terfenadine, astemizole, theophylline, cisapride and digoxin</td>
<td>Avoid estolate in liver disease Care when hepatic dysfunction Excreted in human milk</td>
</tr>
<tr>
<td>Flucloxacillin Dicloxacillin and Cloxacillin</td>
<td>Gut upsets</td>
<td>Probenecid increases blood level</td>
<td></td>
</tr>
<tr>
<td>Penicillins used for infections with penicillinase-forming staphylococci (250–500 mg four times daily)</td>
<td>Morbilliform eruptions</td>
<td>Reduces excretion of methotrexate</td>
<td>Accumulate in renal failure Atopics may be at increased risk of hypersensitivity reactions</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Gut upsets</td>
<td>Potentiates effects of warfarin, phenytoin and lithium</td>
<td></td>
</tr>
<tr>
<td>1 Anaerobic infections (400 mg three times daily)</td>
<td>Metallic taste</td>
<td>Drugs that induce liver enzymes (e.g. rifampicin, barbiturates, griseofulvin, phenytoin, carbamazepine, and smoking) increase destruction of metronidazole in liver and necessitate higher dosage</td>
<td>Use lower dose in presence of liver disease Neurotoxicity more likely if central nervous system disease Carcinogenic and mutagenic in some non-human models</td>
</tr>
<tr>
<td>2 Stubborn rosacea (200 mg twice daily)</td>
<td>Candidiasis</td>
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<tr>
<td>3 Trichomoniasis (200 mg three times daily for 7 days)</td>
<td>Ataxia and sensory neuropathy</td>
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<tr>
<td>Minocycline</td>
<td>Gut upsets</td>
<td>May impair absorption of oral contraceptives</td>
<td>Avoid in pregnancy and in children under 12 years</td>
</tr>
<tr>
<td>A tetracycline used for acne and rosacea (50 mg daily or</td>
<td>Dizziness and vertigo</td>
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Continued p. 342
<table>
<thead>
<tr>
<th><strong>Main dermatological uses and usual adult doses</strong></th>
<th><strong>Adverse effects</strong></th>
<th><strong>Interactions</strong></th>
<th><strong>Other remarks</strong></th>
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<tbody>
<tr>
<td>twice daily, or 100 mg daily in a modified release preparation)</td>
<td>Candidiasis</td>
<td>May potentiate effect of warfarin</td>
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<tr>
<td>Tetracycline and oxytetracycline</td>
<td>Deposition in bones and teeth of fetus and children</td>
<td></td>
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</tr>
<tr>
<td>Acne and rosacea (250–500 mg twice daily)</td>
<td>Deposition in skin and mucous membranes causes blue-grey pigmentation</td>
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<td></td>
<td>Benign intracranial hypertension</td>
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<tr>
<td></td>
<td>Lupus erythematosus-like syndrome with hepatitis</td>
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<tr>
<td>Penicillin V</td>
<td>Gut upsets</td>
<td>Absorption impaired when taken with food, antacids and iron</td>
<td>Avoid in pregnancy and in children under 12 years</td>
</tr>
<tr>
<td>(phenoxymethylpenicillin)</td>
<td>Candidiasis</td>
<td>Many impair absorption of oral contraceptives</td>
<td>Should not be used if renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Rashes</td>
<td>May potentiate effect of warfarin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deposition in bones and teeth of fetus and children</td>
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<tr>
<td></td>
<td>Rare phototoxic reactions</td>
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<tr>
<td></td>
<td>Benign intracranial hypertension</td>
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<tr>
<td>Antifungals</td>
<td>Gut upsets</td>
<td>Blood level increased by probenecid</td>
<td>Accumulates in renal failure</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Morbilliform rashes</td>
<td>Reduces excretion of methotrexate</td>
<td>Atopics at increased risk of hypersensitivity reactions</td>
</tr>
<tr>
<td>Dermatophyte infections when systemic treatment appropriate (as a result of site, severity or extent)</td>
<td>Urticaria</td>
<td></td>
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</tr>
<tr>
<td>Has replaced griseofulvin as first-choice systemic and fungal agent. Unlike itraconazole and fluconazole its action does not involve cytochrome P-450 dependent enzymes in the liver</td>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose: 250 mg daily</td>
<td>Anaphylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea pedis: 2–6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea corporis: 4 weeks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tinea unguium: 12 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Main dermatological uses and usual adult doses

<table>
<thead>
<tr>
<th>Medication</th>
<th>Main dermatological uses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin</td>
<td>Has largely been superseded by newer antifungals</td>
<td>Gut upsets, Headaches, rashes, photosensitivity</td>
<td>Induces microsomal liver enzymes and so may increase elimination of drugs such as warfarin and phenobarbital</td>
<td>Not for use in pregnancy, liver failure, porphyria or systemic lupus erythematosus. Men should not father children within 6 months of taking it. Absorbed better when taken with fatty foods.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>1 Candidiasis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute/recurrent vaginal (single dose of 150 mg)</td>
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<tr>
<td>Mucosal (not vaginal) conditions (50 mg daily)</td>
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<tr>
<td>Oropharyngeal: 7–14 days</td>
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<tr>
<td>Oesophagus: 14–30 days</td>
<td></td>
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</tr>
<tr>
<td>Systemic candidiasis—see manufacturer’s instructions</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>2 Second-line treatment in some systemic mycoses, e.g. cryptococcal infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Dermatophyte infections (except of nails) and pityriasis versicolor (50 mg daily for 2–6 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Candidiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal (200 mg twice daily) for 1 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal (100 mg daily) for 15 days</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2 Pityriasis versicolor (200 mg daily) for 7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Dermatophyte infections (100 mg daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea pedis and manuum for 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinea corporis for 15 days</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tinea of nails—an intermittent regimen can be used (200 mg twice daily for 1 week per month, continued for three or four cycles)</td>
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</tr>
</tbody>
</table>

Continued p. 344
<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>As with fluconazole but greater incidence of liver toxicity</td>
<td>Same as fluconazole</td>
<td>Seldom used in UK. Monitor liver function continually if used for longer than 14 days. Chosen because of its cheapness</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Unpleasant taste Gut upsets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Recurrent vulval and perineal candidiasis</td>
<td></td>
<td></td>
<td>Not absorbed and when given by mouth acts only on bowel yeasts</td>
</tr>
<tr>
<td>2 Persistent gastrointestinal candidiasis in immunosuppressed patients (500 000 units three times daily)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Antivirals**

Aciclovir, famciclovir and valaciclovir
(for dosages see specialist literature)
Famciclovir and valaciclovir have the advantage that they need be taken only two or three times a day
1 Severe herpes simplex infections—primary or recurrent
2 Severe herpes zoster infections—use may reduce incidence of post-herpetic neuralgia
3 Prophylaxis for recurrent herpes simplex especially in the immunocompromised, to treat eczema herpeticum and to treat chickenpox in the immunocompromised

Rapid gut upsets, transient rise in urea and creatinine in 10% of patients after intravenous use
Raised liver enzymes
Reversible neurological reactions
Decreases in haematological indices

Excretion may be delayed by probenecid
Lethargy when intravenous aciclovir given with zidovudine

Adequate hydration of patient should be maintained
Risk in pregnancy unknown
Reduce dose in renal impairment
No effect on virus in latent phase
Must be given early in acute infections

**Antihistamines**

All those listed here are H1-blockers though some dermatologists combine these with H2-blockers in recalcitrant urticaria

Non-sedative

Used for urticaria and type I hypersensitivity reactions

Adequate hydration of patient should be maintained
Risk in pregnancy unknown
Reduce dose in renal impairment
No effect on virus in latent phase
Must be given early in acute infections
### Main dermatological uses and usual adult doses

<table>
<thead>
<tr>
<th>Loratadine and desloratadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Loratadine, 10 mg daily; desloratadine, 5 mg daily)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cetirizine and levocetirizine</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cetirizine, 10 mg daily; levocetirizine, 5 mg daily)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fexofenadine (a metabolite of terfenadine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–180 mg daily</td>
</tr>
</tbody>
</table>

### Sedative

#### Urticaria, type I

<table>
<thead>
<tr>
<th>Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(promethazine &gt; trimeprazine (alimemazine) &gt; hydroxyzine &gt; chlorphenamine = diphenhydramine = cyproheptadine)</td>
</tr>
</tbody>
</table>

**Anticholinergic effects:**
- dry mouth
- blurred vision
- urinary retention
- tachycardia
- glaucoma

| Potentiate effect of alcohol and central nervous system depressants |
| Potentiate effect of other anticholinergic drugs |

| Increased rate of elimination in children |
| Sedation may be useful in an excited itchy patient |
| Warn of risk of drowsiness when driving or operating dangerous machinery |

#### Chlorpheniramine

| 4 mg three or four times daily |

#### Diphenhydramine

| 25–30 mg four times daily |

#### Hydroxyzine

| 10–50 mg four times daily |

#### Cyproheptadine

| 4 mg four times daily |

#### Promethazine

| 10–25 mg daily to three times daily |

#### Trimeprazine

| 2.5–10 mg once or twice daily |

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*Continued p. 346*
### Main dermatological uses and usual adult doses

<table>
<thead>
<tr>
<th>Anti-androgens</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproterone acetate and ethinylestradiol (UK: Dianette; USA: not available)</td>
<td>As for combined oral contraceptives</td>
<td>Should not be given with other oral contraceptives</td>
<td>Contraindicated in pregnancy. Cyproterone acetate is an anti-androgen and if given to pregnant women may feminize a male fetus. For women of childbearing age, therefore, it must be given combined with a contraceptive (the ethinylestradiol component). Also contraindicated in liver disease, disorders of lipid metabolism, and with past or present endometrial carcinomas. Not for use in males or children.</td>
</tr>
<tr>
<td>1 Acne vulgaris, unresponsive to systemic antibiotics, in women only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Idiopathic hirsutism, one tablet (cyproterone acetate 2 mg, ethinylestradiol 35 mg) daily for 21 days, starting on fifth day of menstrual cycle and repeated after a 7-day interval. Treat for 6 months at least</td>
<td></td>
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</tr>
</tbody>
</table>

| Drospirenone and ethinylestadiol (USA: Yasmin; UK: not available) | Hyperkalaemia | NSAIDS and ACE inhibitors increase risk of hyperkalaemia | Contraindicated if abnormal renal or hepatic function. Drospirenone is an analogue of spironolactone. Avoid in pregnancy. May feminize male fetus. Avoid in pregnancy. Causes gynaecomastia. Avoid if renal or hepatic impairment. |
| Spironolactone 25–50 mg daily for idiopathic hirsutism Used in USA | Hyperkalaemia | Increases shelf life of digoxin | |

### Immunosuppressants

<table>
<thead>
<tr>
<th>Azathioprine</th>
<th>Gut upsets</th>
<th>Increased toxicity if given with allopurinol</th>
<th>See comment about the need to check for thiopurine methyltransferase levels (in first column)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For autoimmune conditions, e.g. systemic lupus erythematosus, pemphigus and bullous pemphigoid—often used to spare dose of systemic steroids (1–2.5 mg/kg daily). We strongly</td>
<td>Bone marrow suppression, usually leucopenia or thrombocytopenia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
recommend checking thiopurine methyltransferase levels before starting treatment with azathioprine as homozygotes for the low-activity allele have a high risk of bone marrow suppression.

Cyclosporin

<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
</table>
| 1 Severe psoriasis when conventional treatment is ineffective or inappropriate | Hepatic and renal impairment | 1 Drugs that may increase nephrotoxicity
Hypertension | (See BNF and PDR for fuller details) (Use with tacrolimus specifically contraindicated) |
| 2 Short-term (max. 8 weeks) treatment of severe atopic dermatitis when conventional treatment ineffective or inappropriate (2.5 mg/kg daily in two divided doses). See p. 61 for guidance in use | Gut upset | • Antibiotics (aminoglycosides, co-trimoxazole) |
| | Hypertrichosis | • Non-steroidal anti-inflammatory drugs |
| | Gum hyperplasia | • Melphalan |
| | Tremor | 2 Drugs that may increase cyclosporin blood level (by cytochrome P-450 inhibition) |
| | Hyperkalaemia | • Antibiotics (erythromycin, amphotericin B, cephalosporins, doxycycline, aciclovir) |
| | Occasionally facial oedema, fluid retention and convulsions | • Hormones (corticosteroids, sex hormones) |
| | Hypercholesterolaemia | • Diuretics (frusemide/furosemide thiazides) |
| | Hypomagnesia | • Other (warfarin, H₂ antihistamines, calcium channel blockers, ACE inhibitors) |

Weekly blood checks are necessary for the first 8 weeks of treatment and thereafter at intervals of not longer than 3 months. Reduce dosage if severe renal impairment. Avoid in pregnancy. Possible increased risk of lymphomas.
<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methotrexate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe psoriasis unresponsive to local treatment (initially, 2.5 mg test dose and observe for 1 week, then 5–15 mg once a week orally or intramuscularly)</td>
<td>Gut upsets</td>
<td>Aspirin, probenecid, thiazide diuretics and some non-steroidal anti-inflammatory drugs delay excretion and increase toxicity</td>
<td>Full blood count and liver function tests before starting treatment, and then weekly until therapy is stabilized. Thereafter test every 2–3 months. Avoid in pregnancy Reduce dose if renal or hepatic impairment Folinic acid given concomitantly prevents bone marrow depression Reduced fertility in males Many insist on a liver biopsy before treatment and periodically thereafter as this is the best way of detecting hepatic fibrosis Elderly may be more sensitive to the drug</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>Anti-epileptics, co-trimoxazole, and pyrimethamine increase antifolate effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone marrow depression</td>
<td>Toxicity increased by cyclosporin and acitretin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver or kidney dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Corticosteroids**

<table>
<thead>
<tr>
<th>Prednisone and prednisolone</th>
<th>Impaired glucose tolerance</th>
<th>Liver enzyme inducers (e.g. phenytoin, griseofulvin; rifampicin) reduce effect of corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute and severe allergic reactions, severe erythema multiforme, connective tissue disorders, pemphigus, pemphigoid and vasculitis (5–80 mg daily or on alternate days)</td>
<td>Redistribution of fat (centripetal)</td>
<td>Carbenoxolone and most diuretics increase potassium loss as a result of corticosteroids</td>
</tr>
<tr>
<td>Withdrawal should be gradual for patients who have received systemic corticosteroids for more than 3 weeks or those who have taken high doses</td>
<td>Muscle wasting, proximal myopathy</td>
<td>Corticosteroids reduce effect of many antihypertensive agents</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis and vertebral collapse</td>
<td>Corticosteroids will interact with drugs that affect glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Aseptic necrosis of head of femur</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Growth retardation in children</td>
<td>• Chest X-ray</td>
</tr>
<tr>
<td></td>
<td>Peptic ulceration</td>
<td>• Weight</td>
</tr>
<tr>
<td></td>
<td>Euphoria, psychosis or depression</td>
<td>• Electrolytes</td>
</tr>
<tr>
<td></td>
<td>Cataract formation</td>
<td>• Past history of peptic ulcer, cataracts/glaucoma, and affective psychosis</td>
</tr>
</tbody>
</table>
### Main dermatological uses and usual adult doses

<table>
<thead>
<tr>
<th>Retinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acitretin</strong></td>
</tr>
<tr>
<td>Severe psoriasis, resistant to other forms of treatment (may be used with PUVA, p. 59), palmoplantar pustulosis, severe ichthyoses, Darier’s disease, pityriasis rubra pilaris (0.2–1.0 mg/kg daily)</td>
</tr>
<tr>
<td>Acitretin is not recommended for children except under exceptional circumstances</td>
</tr>
</tbody>
</table>

### Adverse effects

- Precipitation of glaucoma
- Increase in blood pressure
- Sodium and water retention
- Potassium loss
- Skin atrophy and capillary fragility
- Spread of infection
- Iatrogenic Cushing’s syndrome

### Interactions

- Avoid concomitant high doses of vitamin A
- Possible antagonism to anticoagulant effect of warfarin
- Increases plasma concentration of methotrexate
- Increases hepatotoxicity of methotrexate

### Other remarks

1. During treatment check blood pressure, weight, glycosuria, and electrolytes regularly. Patients should carry a steroid treatment card or wear a labelled bracelet. Always bear in mind the possibility of masked infections and perforations.
2. Long-term treatment has to be tapered off slowly to avoid adrenal insufficiency.
3. Do not use for psoriasis or long-term for atopic eczema.
4. Consider the need for adjunctive treatment for osteoporosis.
5. All women of childbearing age must use effective oral contraception for 1 month before treatment, during treatment and for at least 2 years after treatment (see specialist literature for details). Patients should sign a consent form indicating that they know about the danger of teratogenicity.
6. Should not donate blood during or for 1 year after stopping the treatment (teratogenic risk). Regular screening should be carried out to exclude:
   - Abnormalities of liver function
   - Hyperlipidaemia
<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
</table>
| **Isotretinoin** *(13 cis-retinoic acid)*     | Liver function tests:  
↓ Bilirubin  
↑ AST/ALT  
↑ Alkaline phosphatase  
(abnormal in 20% of patients)  
Serum lipids:  
↑ Cholesterol  
↑ Triglycerides  
↓ High-density lipoprotein  
(abnormal in 50% of patients) | See Acitretin | 3 Disseminated interstitial skeletal hyperostosis  
Avoid if renal or hepatic impairment  
Females of childbearing age must take effective contraception for 1 month before treatment is started, during treatment, and for 3 months after treatment is stopped; check pregnancy test(s) before starting treatment and monthly. Females should sign a consent form which states the dangers of teratogenicity (see p. 154 for USA recommendations)  
Before starting a course of isotretinoin, patients and their doctors should know about the risk of the appearance or worsening of depression. The drug should be stopped immediately if there is any concern on this score (see p. 155).  
Avoid in renal or hepatic impairment  
Blood tests as for acitretin | See Acitretin |
<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs acting on the central nervous system (CNS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amitriptyline</strong></td>
<td>Sedation, anticholinergic effects, cardiac dysrhythmias</td>
<td>Potentially lethal CNS stimulation with monoamine oxidase inhibitors</td>
<td>Avoid in the presence of heart disease or hypertension</td>
</tr>
<tr>
<td>1 Depression secondary to skin disease</td>
<td>Confusion in the elderly</td>
<td>Increases effects of other CNS depressants and anticholinergics</td>
<td>Use small doses at first to avoid confusion in the elderly</td>
</tr>
<tr>
<td>2 Post-herpetic neuralgia (50–100 mg at night; start with 10–25 mg in the elderly)</td>
<td>Postural hypotension</td>
<td>Metabolism may be inhibited by cimetidine</td>
<td>Warn about effects on skills such as driving</td>
</tr>
<tr>
<td><strong>Doxepin</strong></td>
<td>See amitriptyline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant with sedative properties sometimes used for antipruritic effect 10–50 mg at bedtime or twice daily</td>
<td></td>
<td></td>
<td>Avoid in breastfeeding</td>
</tr>
<tr>
<td><strong>Diazepam</strong></td>
<td>Sedation</td>
<td>Potentiates effects of other CNS depressants including alcohol</td>
<td>Use for short spells only (to avoid addiction)</td>
</tr>
<tr>
<td>Anxiety—often associated with skin disease (2 mg three times daily)</td>
<td>Impaired skills (e.g. driving) or ataxia</td>
<td>Breakdown inhibited by cimetidine and propranolol</td>
<td>Avoid in pregnancy and breastfeeding</td>
</tr>
<tr>
<td></td>
<td>Dependence (withdrawal may lead to sleeplessness, anxiety, tremors)</td>
<td>Liver enzyme inducers (e.g. phenytoin, griseofulvin, rifampicin) increase elimination</td>
<td>Use with care in presence of liver, kidney or respiratory diseases, and in the elderly</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adrenaline (epinephrine) injection</strong></td>
<td>Tachycardia</td>
<td>If given with some β-blockers may lead to severe hypertension</td>
<td>Do not confuse the different strengths</td>
</tr>
<tr>
<td>Emergency treatment for acute anaphylaxis 0.5 mg (0.5 ml of 1 in 1000 solution given as a slow subcutaneous or, rarely, intramuscular injection. May be repeated after 10 min if necessary)</td>
<td>Cardiac dysrhythmias</td>
<td></td>
<td>Give slowly, subcutaneously or intramuscularly, but not intravenously, except in cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypokalaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Continued p. 352*
<table>
<thead>
<tr>
<th>Main dermatological uses and usual adult doses</th>
<th>Adverse effects</th>
<th>Interactions</th>
<th>Other remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dapsone</strong>&lt;br&gt;Leprosy, dermatitis herpetiformis, vasculitis, pyoderma gangrenosum (50–150 mg daily)</td>
<td>Haemolytic anaemia&lt;br&gt;Methaemoglobinaemia&lt;br&gt;Headaches&lt;br&gt;Lethargy&lt;br&gt;Hepatitis&lt;br&gt;Peripheral neuropathy&lt;br&gt;Exfoliative dermatitis&lt;br&gt;Toxic epidermal necrolysis&lt;br&gt;Agranulocytosis&lt;br&gt;Aplastic anaemia&lt;br&gt;Hypoalbuminaemia</td>
<td>Reduced excretion and increased side effects if given with probenecid</td>
<td>Regular blood checks necessary (weekly for first month, then every 2 weeks until 3 months, then monthly until 6 months and then 6-monthly)&lt;br&gt;Not felt to be teratogenic, but should not be given during pregnancy and lactation if possible. For dermatitis herpetiformis, a gluten-free diet is preferable at these times&lt;br&gt;Avoid in patients with glucose 6-phosphate dehydrogenase deficiency (screen for this, especially in USA)</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong>&lt;br&gt;Systemic and discoid lupus erythematosus, polymorphic light eruption: 200–400 mg daily, maintaining level at lowest effective dose. Must not exceed 6.5 mg/kg body weight/day (based on the ideal/lean body weight and not on the actual weight of the patient)</td>
<td>Retinopathy which may cause permanent blindness&lt;br&gt;Corneal deposits&lt;br&gt;Headaches&lt;br&gt;Gut upsets, pruritus and rashes&lt;br&gt;Worsening of psoriasis&lt;br&gt;Vivid dreams</td>
<td>Should not be taken at the same time as other antimalarial drugs&lt;br&gt;May raise plasma digoxin levels&lt;br&gt;Potential neuromuscular toxicity if taken with gentamycin, kanamycin, or tobramycin&lt;br&gt;Bioavailability decreased if given with antacids</td>
<td>In the UK, before treatment, patients should be asked about their visual acuity (not corrected with glasses). If it is impaired, or eye disease is present, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist. The visual acuity of each eye should be recorded using a standard reading chart. In the USA all patients should have a pre-treatment ophthalmological assessment</td>
</tr>
<tr>
<td>Main dermatological uses and usual adult doses</td>
<td>Adverse effects</td>
<td>Interactions</td>
<td>Other remarks</td>
</tr>
<tr>
<td>------------------------------------------------</td>
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</tr>
<tr>
<td>8-Methoxypsoralen (methoxsalen)</td>
<td>Nausea</td>
<td>Avoid other photosensitizers (Chapter 16)</td>
<td>During treatment, patients should be asked annually about visual symptoms and their visual acuity should be monitored using the standard reading chart. Discontinue drug if any change occurs. Reduce dose with poor renal or liver function. Best avoided in the elderly and children. Do not give automatic repeat prescriptions. Prefer intermittent short courses to continuous treatment if possible.</td>
</tr>
<tr>
<td>Used usually with UVA as PUVA therapy (p. 59)</td>
<td>Itching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe psoriasis, vitiligo, localized pustular psoriasis, cutaneous T-cell lymphoma; rarely, lichen planus, atopic dermatitis</td>
<td>Photoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablets: 0.6–0.8 mg/kg body weight taken as a single dose 1–2 h before exposure to UVA</td>
<td>Catracts</td>
<td></td>
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</tr>
<tr>
<td>Liquid (Ultra Capsules) (USA): 0.3 mg/kg body weight taken 1 h before exposure to UVA</td>
<td>Lentigines</td>
<td></td>
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<tr>
<td></td>
<td>Ageing changes of skin</td>
<td></td>
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<tr>
<td></td>
<td>Hyperpigmentation</td>
<td></td>
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<tr>
<td></td>
<td>Cutaneous neoplasms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main dermatological uses and usual adult doses</td>
<td>Adverse effects</td>
<td>Interactions</td>
<td>Other remarks</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Patients must protect skin against additional sun exposure after ingestion</td>
<td>Monitor eyes for development of cataracts</td>
<td>Try to avoid maintenance treatment, more than 250 treatments and a cumulative dose of more than 1000 joules/cm² (skin cancer risk)</td>
<td></td>
</tr>
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