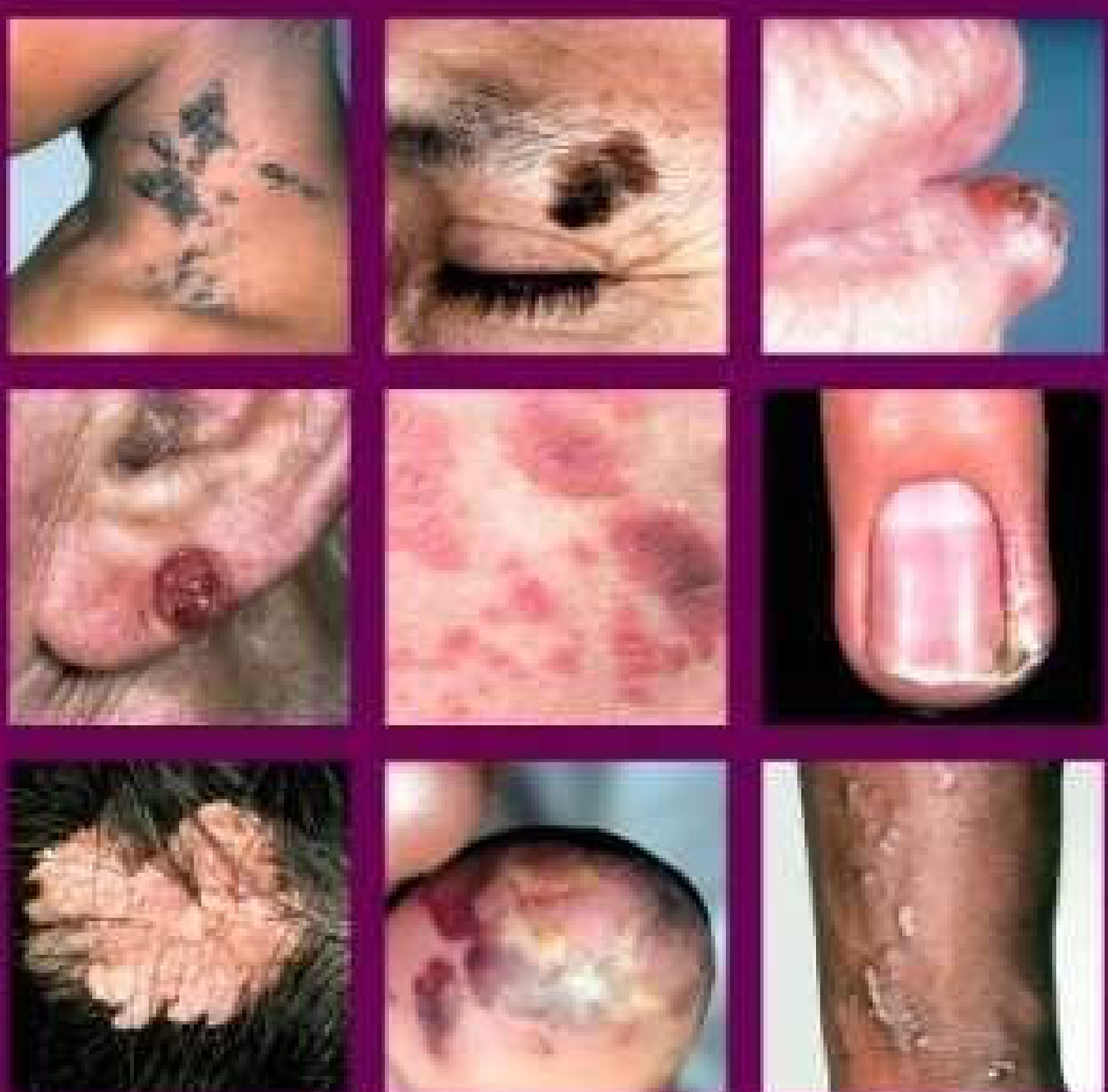
Anthony du Vivier

ATLAS OF CLINICAL DERMATOLOGY

FOURTH EDITION



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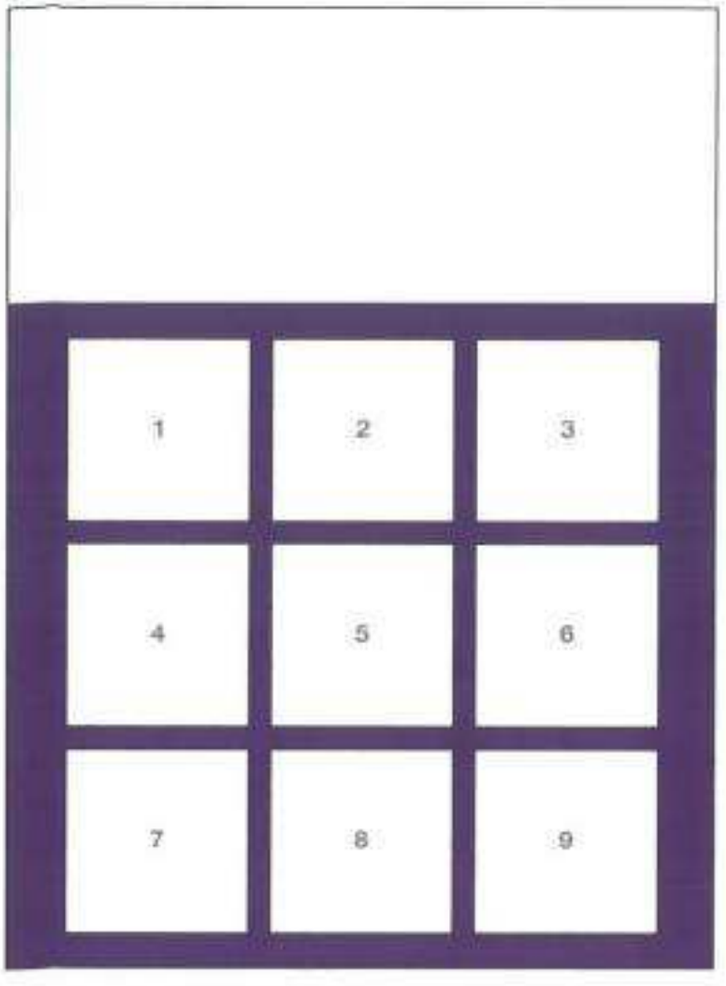
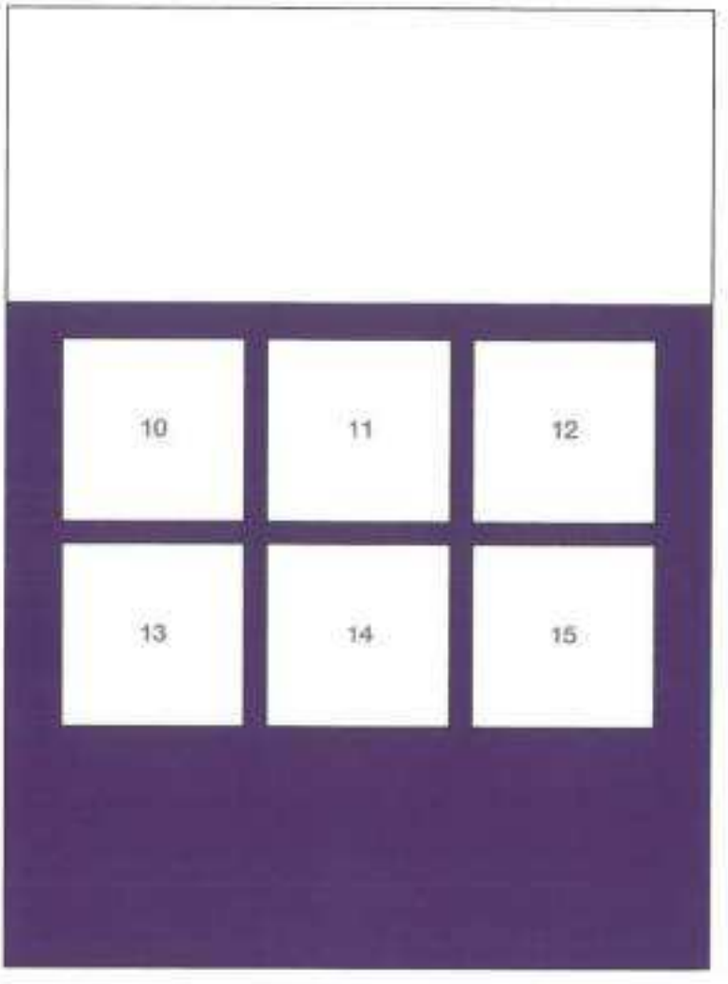
Front Cover



1 Epidermal naevus
2 Superficial spreading malignant melanoma
3 Squamous cell carcinoma of the lip
4 Squamous cell carcinoma of the ear lobe
5 Psoriasis
6 Chronic paronychia
7 Naevus sebaceous
8 Subacute bacterial endocarditis
9 Lichen planus

Back Cover



10 Keratoacanthoma
11 Purpura
12 Psoriatic nails
13 Bullous pemphigoid
14 Candidiasis
15 Psoriasis

Endpapers: Normal sebaceous glands

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ATLAS OF CLINICAL DERMATOLOGY

FOURTH EDITION

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This book is dedicated to a special lady, Judith Brett, who is both my lovely wife and favourite doctor.

"Age cannot wither her, nor custom stale
Her infinite variety"

ANTONY AND CLEOPATRA, ACT II, SCENE 2, 243–4.

Preface

The first edition of this Atlas of Clinical Dermatology was a collection of over 1500 colour illustrations of common skin disorders accompanied by a series of essays on their clinical features. It attracted a wider audience than I had anticipated in that it appeared to be of interest to both generalists and dermatologists. I therefore completely revised the text of the second edition with both in mind. Each condition was defined and its aetiology, clinical features and pathology discussed. The management of the common disorders was described in considerably more detail so that the book could be of practical as well as diagnostic value to those in family practice. Rarer disorders were added and illustrated for the benefit of the dermatologist in training. In the third edition, the chapters on cutaneous manifestations of reactive, developmental and systemic processes were greatly expanded to broaden the appeal for the internist and dermatologist, and those on naevi, malignant melanoma and other skin tumours were increased in size for the surgeon. In this edition my publisher, Sue Hodgson, requested that I put the book on a diet and reduce its size. I would not have done it for anyone else but have given in despite one charming New York reviewer comparing the 3rd edition to a ⅓-lb extra lean pastrami sandwich on rye. The number of illustrations however remain at approximately 2400 and many new ones have been added. Where possible, I have tried to compare conditions in both black and white skins.

Acknowledgements for the fourth edition

I have acknowledged in the third edition my mentors and colleagues who have meant so much to me in dermatology. In the final chapters of my career, more house physicians, registrars and consultants have come my way whom I respect and who are now or about to become great dermatologists. They are Genevieve Osborne, Deirdre Buckley, Kate Short, Nuala O'Donaghue, Karen Watson, Jonathan White, Sarah Macfarlane, Claire Martyn Simmonds, Sasha Dhoat, Aileen and Saqib Bashir, Ferina Ishmail, Rishika Sinha, Emma Craythorne, Emma Benton, Sacha Goolamali, Victoria Hogarth, John Ferguson and Sarah Walsh.

Many dermatologists have the privilege of collaborating with physicians from other specialties. My pleasure has been to work with the department of haemato-oncology at King's under the leadership of Professor Ghulam Mufti, the finest scientist and physician I have ever met. Also, Dr Jon Salisbury is our first class pathologist at King's and he has updated some of Dr Philip McKee's excellent work on pathology in Chapters 2 and 9.

Elsevier has been good to me. Sue Hodgson, who commissioned the fourth edition, remains a good friend. Rus Gabbedy has been utterly charming throughout despite my impossibly demanding nature. Sven Pinczewski, Ruth Noble, Lucy Boon, Caroline Jones, Christian Bilbow and Marion Stockton have been wonderful to work with and Sharon Nash who orchestrated the finer details of the project has done her native Manhattan proud.

Finally, I belong to a generation, which cannot survive without an efficient and sympathetic secretary. Annette Norey continues to manage me and my Wimpole Street practice in central London with great aplomb. Monica Braithwaite has taken special care of me and my needs at King's College Hospital. I salute and thank them both.

Acknowledgements from the third edition

I have in the first edition acknowledged the deep gratitude I have to the physicians who taught me dermatology. In particular, without the encouragement and example of Dr Dowling Munro and the late Dr Peter Borrie at St Bartholomew's Hospital, London, I might have missed dermatology and been an unhappy man. Dr Richard Stoughton introduced me to the laboratory side of the subject at the Scripps Clinic and Research Foundation in La Jolla, California, and was generous in opening up the exciting world of American dermatology to me. Since my consultant appointment at King's College Hospital, London, I have been greatly helped by my colleagues Drs Andrew Pembroke, Elisabeth Higgins, Claire Fuller and Daniel Creamer, and I am particularly grateful to them for their forbearance and support whilst I have been writing these books. I have also been particularly fortunate in having a series of excellent registrars to work with at King's who are all now Consultants, but I would like to acknowledge how good they have been to me, and they include Drs Barry Monk, Michèle Clement, Sallie Neill, Jenny Hughes, Olivia Schofield, Stephanie Munn, Pamela Todd, Noreen Cowley, Lindsay Whittam, Karen Harman, Fiona Child, Fiona Keane and Professor Hywel Williams.

The majority of illustrations are, unless otherwise stated, of patients under the care of myself or members of the Dermatology Department at King's College Hospital, London. The photographs have largely been taken by the Medical Illustration Department of King's College Hospital. The rest have come from photographic departments of the hospitals where I trained, viz St Bartholomew's, St Mary's and St John's, London, and my own collection. I particularly wish to thank, therefore, Mr E. Blewitt, Mr D. Tredinnnick, Dr P. Cardew, Mr B. Pyke, Mr E. Sparkes, Mr S. Robertson, Yvonne Bartlett, David Langdon, Lucy Wallace, Margaret Delaney and Alex Dionysiou for the help they have given me over the years.

I am once again indebted to Dr Phillip McKee for his help in providing me with illustrations of the pathology. He is an exceptionally delightful, generous and special man. Other pathologists who have been particularly helpful to me during the course of my work at King's are Dr Jon Salisbury and Dr Debbie Hopster. They have taught me that it is impossible to practise medicine without the backing of the pathologists. Elsevier Health Sciences have provided a team that I have really enjoyed working with. Sue Hodgson has been an outstanding editor. It is not easy to completely revise a textbook and combine this with a busy medical practice. Most editors would have been exasperated as each deadline passed, but her charm, patience and tact cajoled me ultimately into delivery. Quite probably my salvation lay in her happiness at becoming engaged and I can vouch for the fact that her fiancé is a lucky man. Louise Cook stage-managed the early part of the project and Scott Millar was a pleasure to work with as he went through each proof with me late into the evening and orchestrated the production of the final product.

Finally, I would not have been able to write these books in the first place were it not for the skills of two superlative secretaries: Mrs Annette Norey who has run the London practice of my friend Dr Jeremy Gilkes and myself with masterly efficiency and understanding for 30 years and probably knows more about dermatology than most doctors; and Miss Pauline Johnson who ran the skin department at King's for 3 years before she returned to her native Scotland and subsequently found a charming dermatology registrar to marry, Dr Colin Morton, now a Consultant at Falkirk Royal Infirmary. Pauline has retyped the whole of the 3rd Edition at home in Scotland with her mother helping out by babysitting for Penny, Jack and Zoe.

Contents

The dermatological diagnosis 1

The 'spot diagnosis' is a delusion, a belief strongly adhered to by medical students and others despite its obvious deficiencies. It is always impressive to see an experienced dermatologist arrive seemingly instantly at a diagnosis but, just as Sherlock Holmes astounded Dr Watson with observations regarding his life history at their first encounter in the pathology department at St Bartholomew's Hospital, it is a matter of a series of careful observations that result in correct deduction. Just as no one would approach a cardiologist, proffer a radial pulse and expect a diagnosis, so it is not enough to 'glance' at an eruption and expect to make a diagnosis. Surprisingly, this is a common request from colleagues, often in dimly lit corridors – a practice aptly referred to as 'kerbside dermatology'. Like any other branch of medicine, dermatology is a science and diagnosis results from detailed history taking, thorough examination and accurate observation. It is essential that this should take place in consulting rooms with plenty of natural sunlight affording good illumination. A British winter's evening is an anathema for examining the skin.

The teaching of dermatology varies. Some medical schools have excellent training programmes, but others do not teach undergraduates dermatology at all; sometimes the course is optional. This is regrettable, because approximately 20% of consultations in family practice relate to the skin. Even in good centres, medical students will not have enough exposure to the diagnosis and management of skin disorders, for understandably their time is limited. It is, therefore, an excellent idea to spend time as a postgraduate with the local dermatologist. The problem with dermatology is its visibility and the fact that the conditions were codified many years ago in ancient languages that are no longer learnt at school. This nomenclature gives rise to confusion. Nonetheless, with the gradual elucidation of the aetiology of each skin disorder and the major advances being made in therapy, the field is rapidly expanding and has already given rise to specialists within the speciality.

The history

Taking the history of a skin disorder is usually a less prolonged affair than in general medicine. Indeed, sometimes it is more productive to examine the skin early in the consultation to get some idea of the problem and then to proceed to ask the relevant questions.

General Questions

How long has it been present? Some eruptions begin acutely (e.g. drug eruptions), whereas others are more insidious (e.g. pityriasis versicolor).

How does it behave? Some disorders are liable to relapse and remit. For example, a diagnosis of urticaria, which may not be visible on the day of the consultation, may be made from a characteristic history of red, itchy swellings that appear anywhere on the skin and disappear without trace within 24 hours. Factors relating to the relapses may be important (e.g. exposure to bright sunlight may precipitate recurrent attacks of herpes simplex). Some disorders evolve through different stages, classically chickenpox. Others result in crops of lesions (e.g. lymphomatoid papulosis, where the initial red-brown papules become haemorrhagic, crusted, necrotic and heal as scars).

How did it start? In pityriasis rosea, a solitary patch appears before a large number of smaller patches appear all over the torso several days later. The single lesion is known as the herald patch and is an important clue to diagnosis.

What did it look like initially? Some patients are very observant and can record the progress of their condition accurately. For example, in impetigo, they note that it starts as blisters, which quickly break and form crusts. Their descriptions may be very helpful if the rash has temporarily disappeared, as happens with urticaria and herpes simplex. Often, however, if it has disappeared, it is wise to suggest that the patient returns immediately when it recurs and has access to an 'SOS appointment' so that the eruption can be seen at its height.

Is it anywhere else? Patients may complain about something they consider important but disregard a long-standing skin condition elsewhere. Thus, an acute weeping eczema on the face may clearly be the prime problem to the patient, but the cause of it may be autosensitization following an allergic contact sensitivity to a cream used to treat chronic varicose eczema on the leg, which is thought to be totally unrelated by the patient. Therefore, all the skin should be examined. Alternatively, the patient may be unaware of a skin eruption elsewhere on the body or be too embarrassed to mention it because of its location.

What affects it? The patient's view is sometimes invaluable. The patient may suspect the sun, the cat, something at work, 'nerves', her menstrual periods or some tablet or food as the cause of the complaint. Often the patient is correct.

Where do you come from? A knowledge of diseases endemic in various parts of the world is useful: a Vietnamese may have erythema nodosum secondary to tuberculosis; a Philippino leprosy and an African onchocerciasis. Certain racial groups are more prone to disease processes, e.g. a West Indian may have sarcoidosis and a Caucasian skin cancer.

Have you been abroad recently and if so where? Foreign travel exposes the patient to diseases that are uncommon in their country of origin. For example, the insect that bit the patient may have been infected with the protozoan *Leishmania* sp. and Baghdad boil (cutaneous leishmaniasis) can occur in less exotic places such as the Mediterranean.

Symptoms

Does it itch? Some disorders always itch (e.g. scabies), and the very intensity of the complaint may suggest the diagnosis. The rash of secondary syphilis virtually never itches. Psoriasis and pityriasis rosea are quixotic and may or may not itch.

Is it painful? Few dermatological disorders are acutely painful, but the classic example is that of herpes zoster. Pain dominates the history (you do not need to ask) and the suspicion is confirmed when the unilateral vesicular eruption is revealed on examination.

Is it sore? An eruption such as eczema or psoriasis may become sore when it dries out and cracks, particularly in cold climatic conditions.

Does it burn? Few skin disorders burn; patients thus afflicted volunteer the symptom. The rash of erythropoietic protoporphyria burns and the localization of the symptoms to the light-exposed skin might suggest the diagnosis. If burning affects the mouth, genitalia or face without any visible physical signs, it is often a psychosomatic symptom.

Associated Symptoms

The skin disorder may follow a prior illness. For example, a streptococcal infection frequently precedes guttate psoriasis, erythema nodosum and Henoch–Schönlein purpura. The rash, however, may result from a drug given to treat an illness (e.g. the unfortunate prescription of ampicillin for a sore throat in a young adult with unsuspected infectious mononucleosis) or the skin rash may be one of the presenting features of a systemic disease (e.g. sarcoidosis or lupus erythematosus). It is important, therefore, to enquire about symptoms relating to other systems.

Past History of Skin and Related Disorders

A past history of skin and related disorders is often relevant. This is particularly relevant to young women who have had eczema in childhood; they may develop it again on the hands, either as a result of an occupation such as hairdressing or when looking after small children. Alternatively, a patient may develop late-onset eczema, with the clue to its cause being other symptoms of atopy such as hay fever or asthma in childhood.

Family History

Many common skin diseases are inherited, including psoriasis, ichthyosis and eczema. Sometimes the patient denies a family history at the initial consultation, but this is usually simply because no one has ever mentioned a skin disorder to them previously. Subsequent questioning at a family reunion may provide information of which the patient was unaware.

Past Medical History

A previous illness may help to explain the present complaint. Thus, a difficult and protracted labour may be responsible for a diffuse loss of hair 3 months later (telogen effluvium). A chronic illness (e.g. diabetes mellitus) might make the patient more prone to a chronic candidal paronychia.

Previous and Current Drug Therapy

Clearly, a systemic agent may be the cause of a skin disorder, such as a phenothiazine, a diuretic or a tetracycline for a phototoxic eruption or an antibiotic for a morbilliform rash. The patient may recall a previous allergic reaction but be unaware that the present medication is a related product. Drugs such as systemic steroids are immunosuppressive and may make a patient more prone to infections with commensals (e.g. pityriasis versicolor). Family practitioners are very good at listing the oral agents in their letters of referral to the specialist, but sometimes topical remedies get forgotten. These are important because the therapy prescribed may have been correct and yet ineffective in a particular patient and there is no point in represcribing the drug.

Conversely, the prescribed therapy may be making the disease worse and patients will often note this. This may be because the condition has been misdiagnosed (e.g. when tinea or rosacea is diagnosed as eczema and treated with steroids). Moreover, a complication may have occurred in a steroid-responsive dermatosis so that the steroid is no longer appropriate, as when molluscum contagiosum is superimposed upon eczema. Equally, the patient may have become sensitized to the prescribed agent; this occurs particularly when varicose eczema is treated with agents containing topical antibiotics (e.g. neomycin). Another possibility is that the patient may have developed an irritant reaction to a drug such as dithranol, which is used in the treatment of psoriasis. Some races like to lighten their skin colour or bleach pigmented marks on their skin; noxious chemicals including steroids can be obtained from the local market for this purpose. Finally, alcohol is a drug that is often forgotten. In sufficient quantity it tends to exacerbate psoriasis, discoid eczema and rosacea.

Occupation

Just as coal miners are prone to pneumoconiosis, so certain occupations predispose to skin disease. Percival Pott established the link between carcinoma of the scrotal skin and previous exposure to soot in men who had cleaned chimneys as children. Dubreuilh pinpointed the relationship of malignant melanoma on the face of the workers in the vineyards of Bordeaux to exposure to ultraviolet light. Exposure to contact allergens at work is often suspected because the patient gets better at the weekend or when away on holiday. This might be so with dermatitis secondary to chromate exposure, which is common in builders who work with cement. Probably the most common occupational skin diseases seen in dermatology are primary irritant dermatitis and chronic candidal paronychia in housewives, nurses and barworkers, caused by the frequent exposure of the hands to water.

Social History

The situation at home is of great importance. Other members of the household may be itching, which may suggest a diagnosis of scabies. The family cat and its cohabitants may be the source of the insect bites. Psychological factors are as critical in skin disorders as they are in other branches of medicine. The unhappiness of a marriage or relationship, guilt (religious or otherwise), success or failure at work or difficult children, all take their toll and it is difficult to manage any chronic skin disease without a knowledge of these problems. It may be that the whole eruption is caused by the patient (dermatitis artefacta) or that the failure to recover is because the patient does not wish to get better, preferring instead to evoke sympathy and attention because of the condition. Sometimes patients simply overreact to a minor skin condition, the presence of which is the final straw in a lifestyle that has got completely out of control.

Effect of the Disease on the Patient

The patient is likely to be anxious regarding the nature of the disorder. Infectivity and malignant disease are the commonest fears so that informed reassurance to the contrary, if appropriate, may be of enormous help to the patient. Sometimes the concern may amount to a phobia, for example regarding herpes simplex in the 1970s and now acquired immunodeficiency syndrome (AIDS); consequently, further psychological help will be required.

The functional effects are important. An eruption on the feet may make it difficult to walk, and one on the hands difficult to work. The appearance of the condition on exposed parts may make the patient feel leprous and ostracized. Extraordinary variations in patients' reactions occur. Some will put up with a considerable degree of psoriasis and yet others will be disgusted and aggrieved by minimal disease. All these factors have to be considered when deciding how aggressively to treat a disorder.

The examination

Ideally the whole patient should be examined. This is not usually necessary for warts, but it is for most conditions. A basal cell carcinoma of the face may be accompanied by other solar-induced malignancies elsewhere, such as a malignant melanoma on the back, an area that the patient cannot easily see; an eruption on one hand may be explained by the spread of tinea from the toenails and feet, and a condition of both hands that is unresponsive to therapy may be due to the psoriasis revealed by examining the elbows and scalp.

It is sensible to examine the skin in an orderly manner, starting at the hands, so as not to miss the burrows of scabies, and then proceeding up the arms, face, trunk and so on. The hair, nails and mouth should not be forgotten.

It is important also to palpate the lesions. Disorders involving primarily the dermis (e.g. sarcoidosis or lymphoma) can be distinguished from those affecting the epidermis (e.g. eczema) because they are palpable. Patients are reassured by a thorough general medical examination. They are relieved that the doctor is prepared to feel their skin because it helps to dispel the fear that their condition makes them 'untouchable'. Finally, the

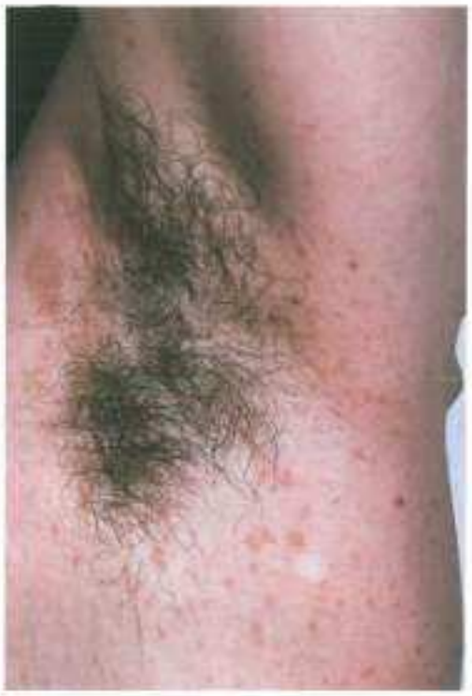


Fig. 1.1 Macules. A macule is a flat lesion less than 1 cm in diameter. Many freckle-like macules are present in the axilla. A larger café-au-lait patch gives away the diagnosis of *neurofibromatosis*.

skin is a part of the whole, and a full general medical examination may be necessary if the patient appears ill or if the cutaneous signs give rise to suspicions of a systemic process.

Vocabulary

Just as râles, rhonchi and bronchial breathing are physical signs that, once elicited, contribute to a pulmonary diagnosis, so there is a dermatological vocabulary that must be grasped to ascertain the nature of a skin disorder. The main types of lesion may be defined as follows.

Primary Lesions

Macule A macule is a circumscribed flat alteration in the colour of the skin which is less than 1 cm in diameter (Figs 1.1 and 1.2). It may be variously coloured, for example pink or red owing to vasodilatation and mild inflammatory changes; purple (Fig. 1.3) or yellow–brown from blood or haemosiderin; or brown, black, pale or white owing to a disturbance in melanin synthesis.

Papule A papule is a circumscribed palpable elevation of the skin less than 1 cm in diameter (others define it as less than 0.5 cm in diameter). A papule may be epidermal (Fig. 1.4), dermal or both in origin. For example, the papules of warts or molluscа contagiosa (Fig. 1.5) are caused by viral parasitosis of epithelial cells, leading to epidermal hyperplasia, whereas

Fig. 1.2 Macules. These hypopigmented macules vary in size and have enlarged by confluence. They are due to a superficial yeast infection, *pityriasis versicolor*.

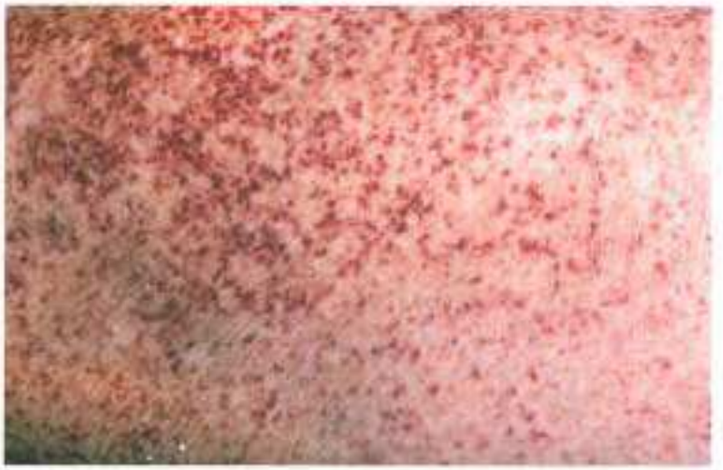


Fig. 1.3 Macules. These tiny macules are purple in colour and do not blanch with pressure. They are known as petechiae. Thrombocytopenia and vasculitis are common causes.

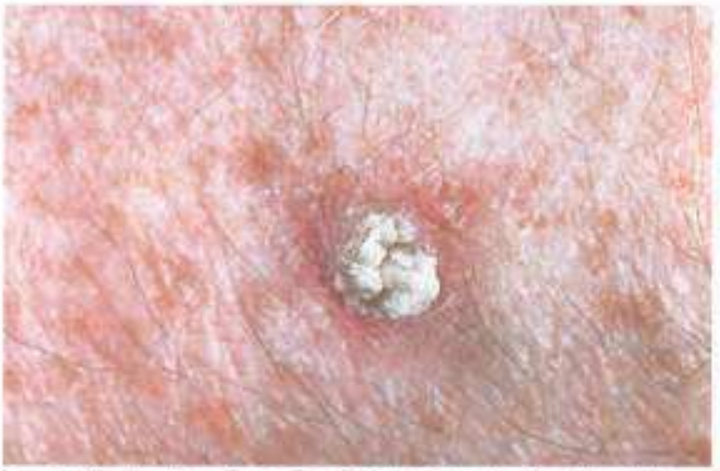


Fig. 1.4 Papule. A papule is a circumscribed palpable elevation of the skin less than 1 cm in diameter. This red papule with an adherent scale is a *solar keratosis*.

Fig. 1.5 Papule. This more or less flesh coloured papule with central dimpling of the surface is caused by *molluscum contagiosum*. Lesions on the face in adults are suggestive of immunodeficiency.

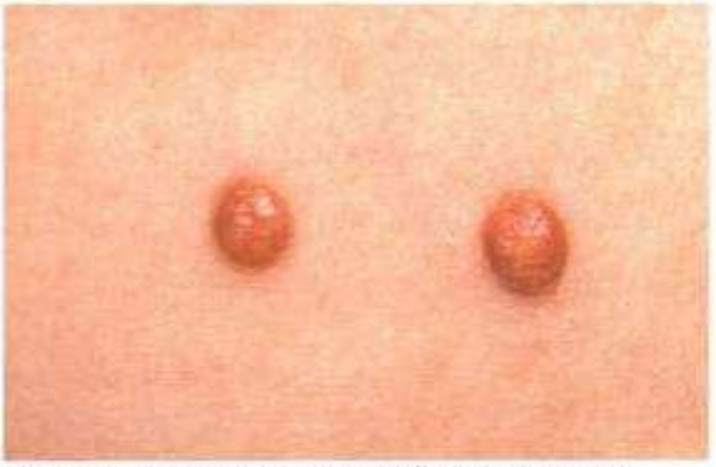


Fig. 1.6 Papules. These lesions are yellow in colour, which suggests the diagnosis of hyperlipidaemia. They are called *xanthomas*.

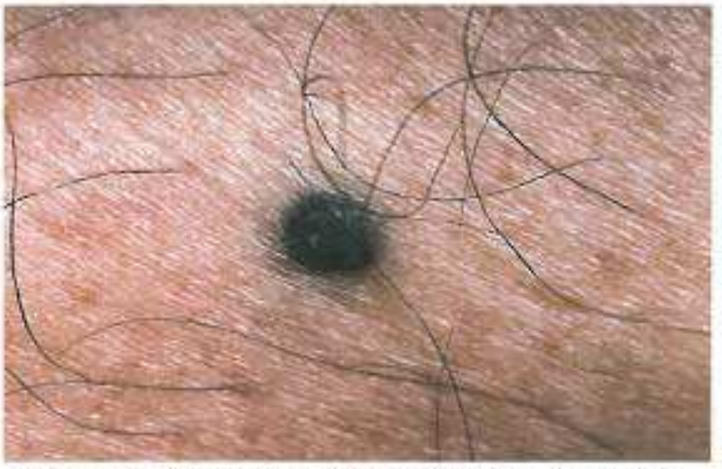


Fig. 1.7 Papule. The bluish hue of this solitary lesion is striking and serves to distinguish it from a malignant melanoma. It is a benign *blue naevus*, often found on the face or back of the hands.

Fig. 1.8 Papule. The history of gradual increase in size and the black colour of this solitary papule suggested the diagnosis of a vertical growth phase invasive *malignant melanoma*.

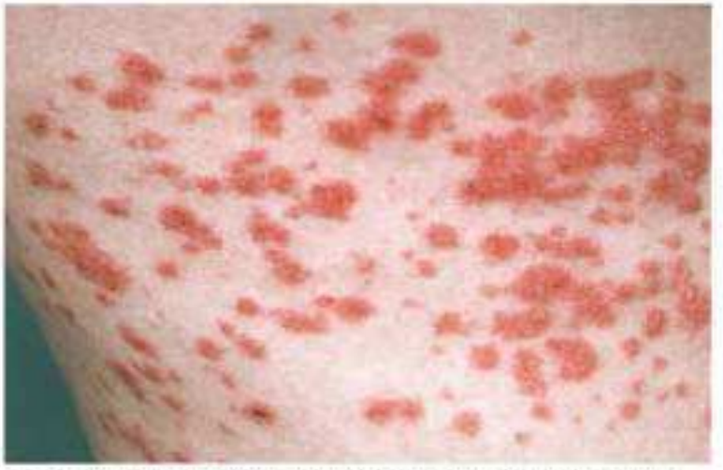


Fig. 1.9 Papules. The deep red colour of these papules is distinctive. Some of the papules have become confluent and formed plaques. This is *psoriasis*.

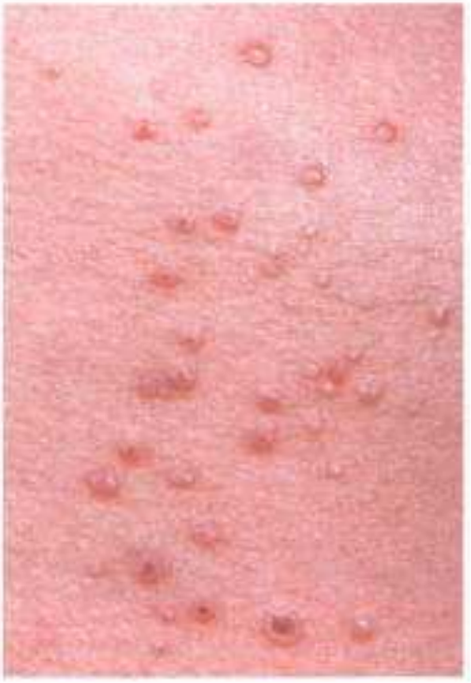


Fig. 1.10 Papules. The purple colour of these papules is distinctive. Their surface is also flat-topped and shiny, permitting a diagnosis of *lichen planus*.

Fig. 1.11 Papules. These papules are flat surfaced and somewhat shiny. Older lesions show hyperpimentation following damage to the basal cell layer of the epidermis by *lichen planus*. The purple colour may be difficult to discern in a black skin.

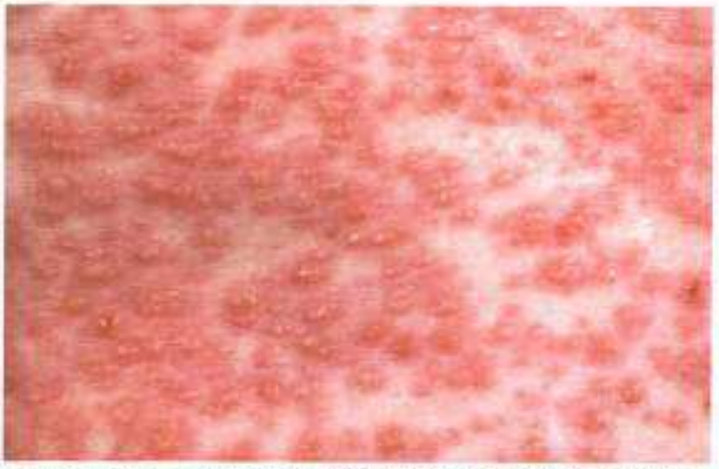


Fig. 1.12 Papules. These papules are red and oedematous and have become confluent with erythematous macules (hence 'maculopapular'). It began ten days after starting a course of ampicillin.

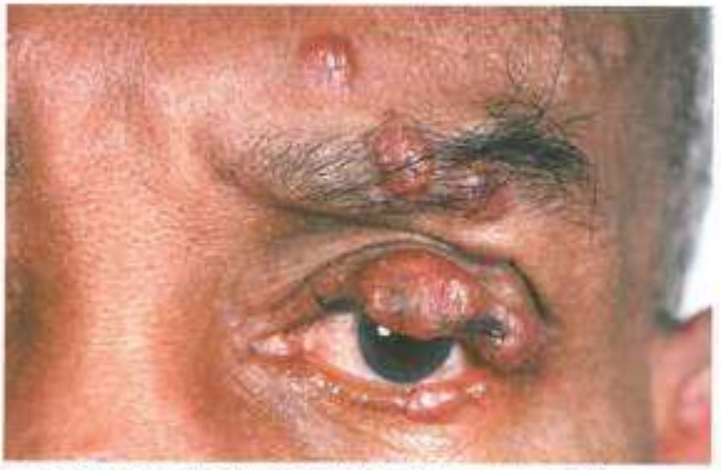


Fig. 1.13 Nodules. The nodules are of different sizes and shapes. The involvement of the eyelids is very characteristic of sarcoidosis. Many skin disorders have a predilection for certain sites on the body.

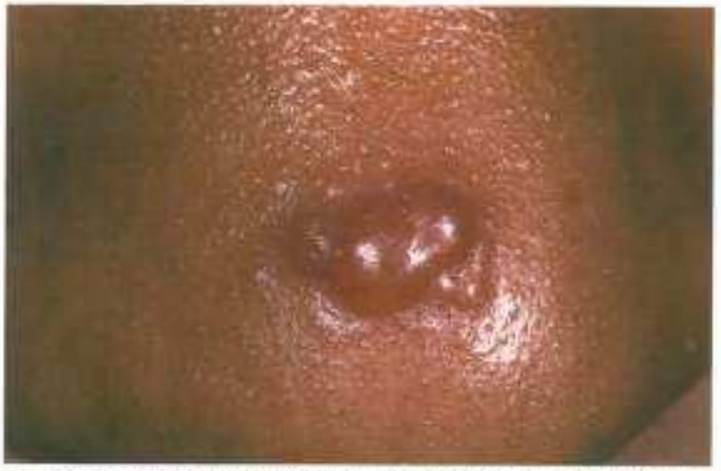


Fig. 1.14 Nodule. This nodule also on the nose of a West Indian is lobulated and red brown in colour, but has an entirely different explanation from the nodule depicted in Fig. 1.13. It was due to *sarcoidosis*.

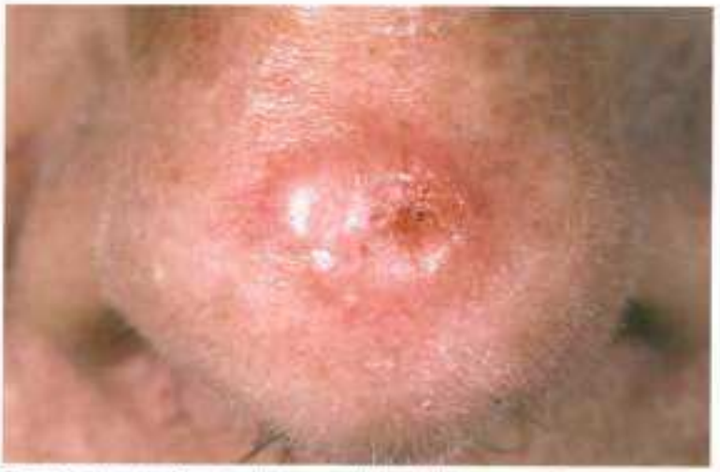


Fig. 1.15 Nodule. This raised circumscribed palpable mass on the nose was greater than 1 cm in diameter and pearly in colour. It bled occasionally and was a *basal cell carcinoma*.

those in which the dermis is involved may be due to deposits of lipid (Fig. 1.6) or collections of benign (Fig. 1.7) or malignant cells (Fig. 1.8). The papules of skin eruptions such as eczema are caused by epidermal oedema (spongiosis), of psoriasis (Fig. 1.9) by increased epidermal cell turnover, and of lichen planus (Figs 1.10 and 1.11) by a lymphocytic infiltrate which involves the upper dermis and epidermal–dermal junction. In a morbilliform drug eruption, there is a mild dermal perivascular infiltrate which gives rise to oedematous lesions clinically (Fig. 1.12).

Nodule A circumscribed palpable mass larger than 1 cm in diameter. The epidermis plus dermis, dermis plus subcutis or subcutis alone may be involved. The lesion may clearly evolve from a papule. The causes are legion but include an infiltrate of granulomas (e.g. sarcoid; Figs 1.13 and 1.14), benign (e.g. a dermatofibroma) or neoplastic cells (e.g. a basal cell carcinoma; Fig. 1.15, keratoacanthoma or squamous cell carcinoma, Fig. 1.16).

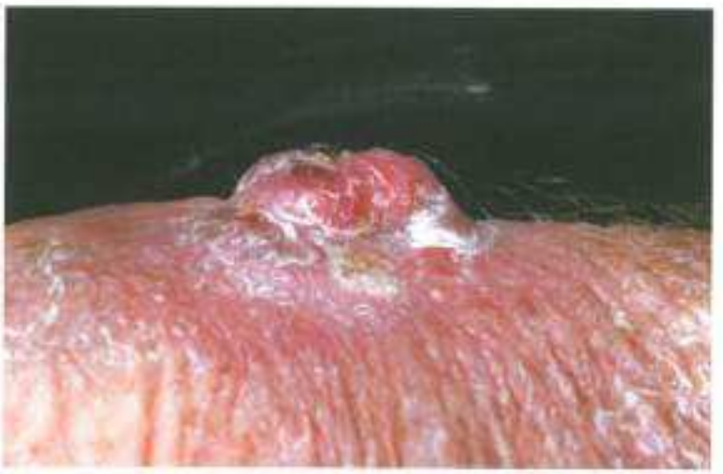


Fig. 1.16 Nodule. There is a red lobular mass arising from a plaque on sundamaged atrophic skin. This is a *squamous cell carcinoma*.

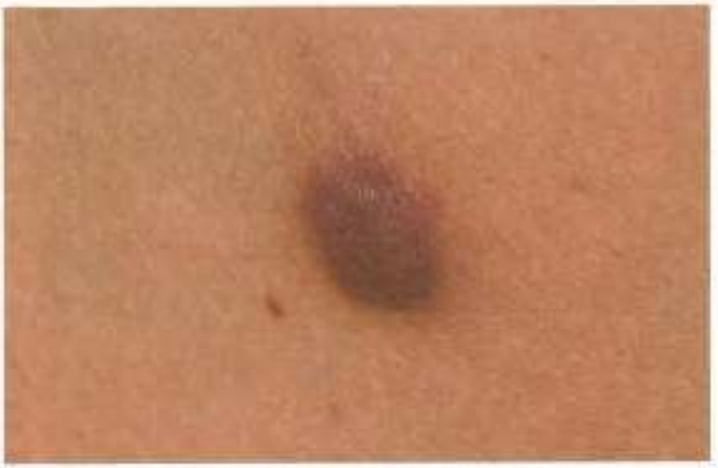


Fig. 1.17 Nodule. This nodule (or tumour) is purple in colour, which is very suggestive of Kaposi's sarcoma. Biopsy establishes the diagnosis. Colour is an important physical sign in dermatology.

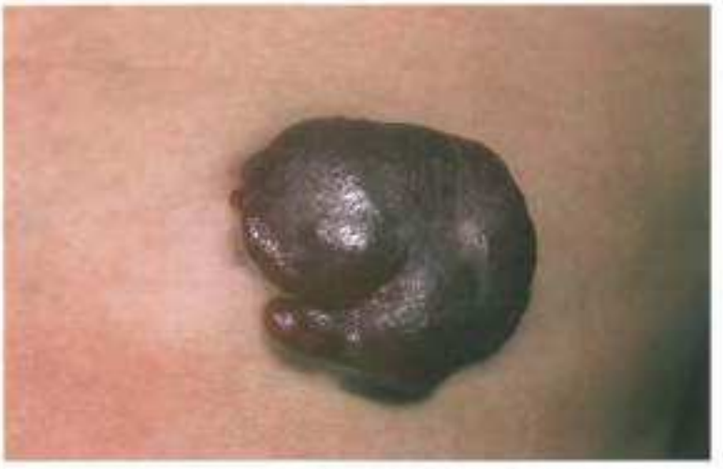


Fig. 1.18 Nodule. This large red and purple lobulated mass grew rapidly shortly after birth and was a *haemangioma*.

inflammation (e.g. erythema nodosum), Kaposi's sarcoma (Fig. 1.17), haemangioma (Fig. 1.18) or lymphoma.

Patch A flat lesion greater than 1 cm in diameter (i.e. a large macule) is known as a patch (Fig. 1.19).

Plaque A slightly raised lesion greater than 1 cm in diameter (Fig. 1.20). Colour (Figs 1.21, 1.22, 1.23 and 1.24), the presence or absence of scaling (Fig. 1.25), changes on the surface (Fig. 1.26) and the shape (Fig. 1.27) may assist in diagnosis. It may be formed by an extension or coalescence of papules, as in psoriasis or granuloma annulare.

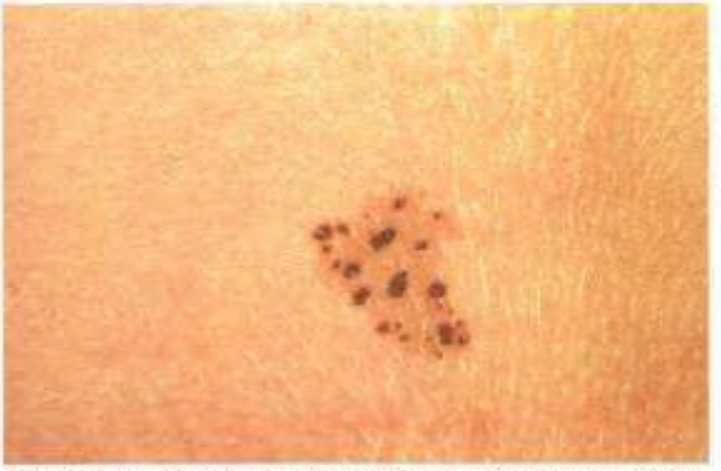


Fig. 1.19 Patch. A patch is a flat lesion greater than 1 cm in diameter. There are small pigmented macules within a light-brown (café-au-lait) patch. This congenital melanocytic lesion is known as *naevus spilus*.

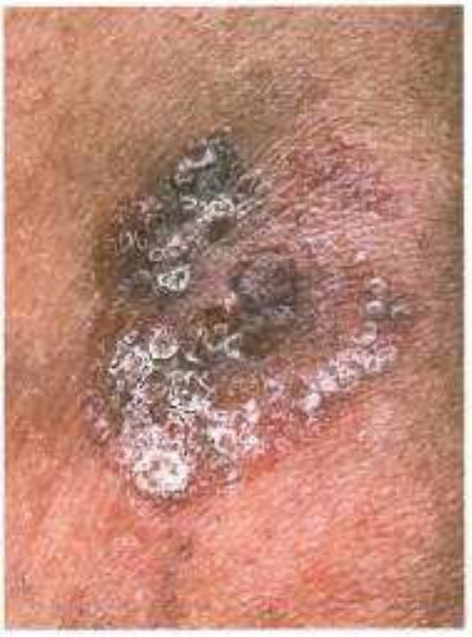


Fig. 1.20 Plaque. Although psoriasiform, this well-defined red plaque was solitary. It was an *intraepidermal carcinoma*.

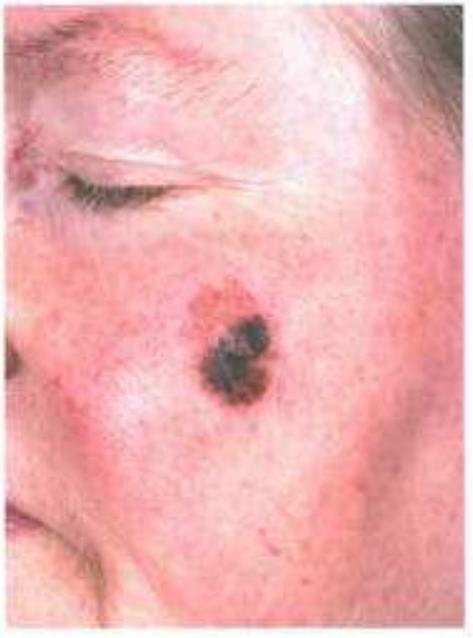


Fig. 1.21 Plaque. The multiplicity of pigmented colours in this *lentigo maligna melanoma* help to clinch the diagnosis. It has evolved from a patch (tan colour) to a plaque (blacker area).

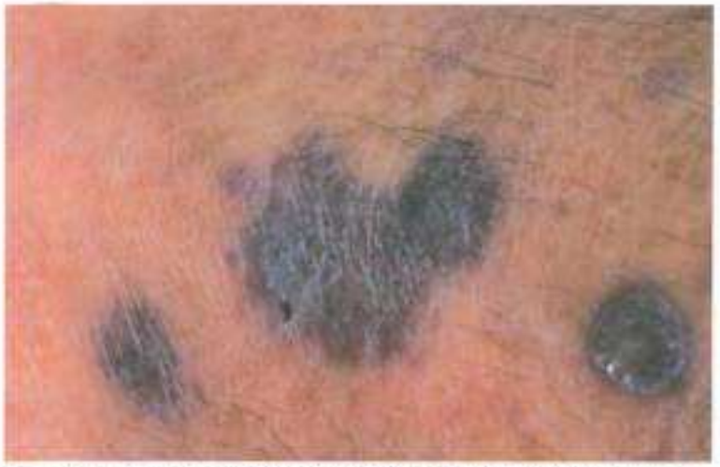


Fig. 1.22 Plaque. These purple raised lesions have evolved from confluence of papules of *lichen planus*. This colour is the characteristic appearance in Asian skin.

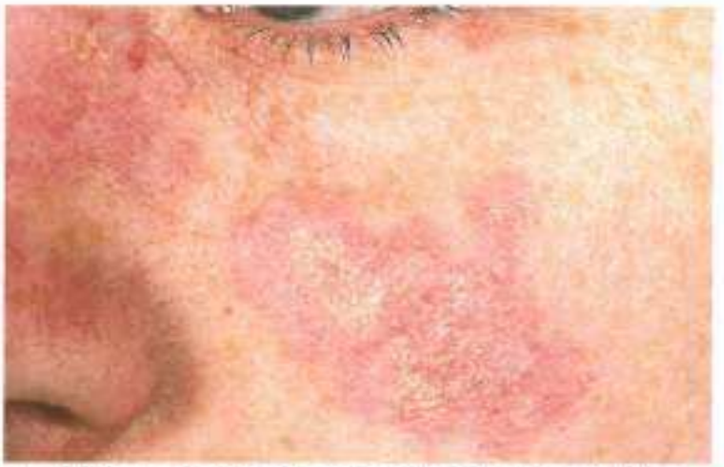


Fig. 1.23 Plaque. The mauve colour and tenacious scale are characteristic of *lupus erythematosus*. Light-exposed areas such as the cheeks are particularly affected.

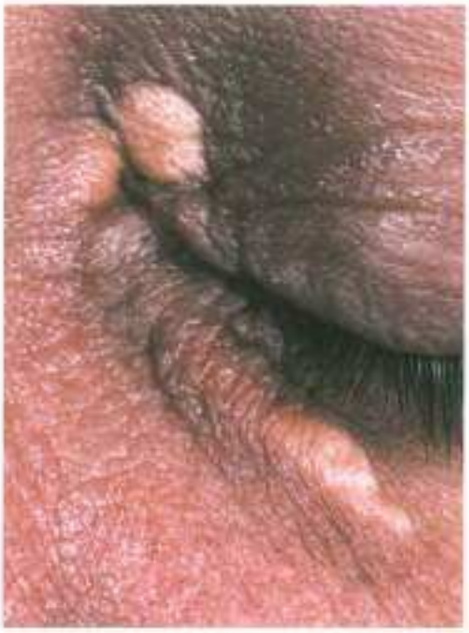


Fig. 1.24 Plaque. This palpable lesion has no surface change, which would suggest that the pathology is in the dermis. The yellow colour and position around the eye is characteristic of *xanthelasma*.

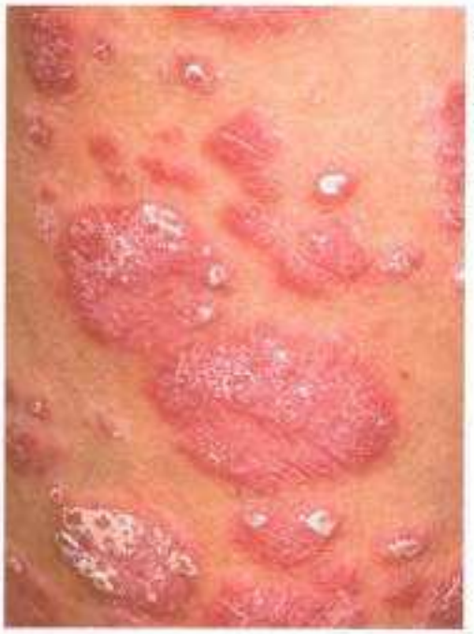


Fig. 1.25 Plaque. Small papules are present but most have enlarged to form well-defined plaques. The deep red colour and thick white scale are typical of *psoriasis*.

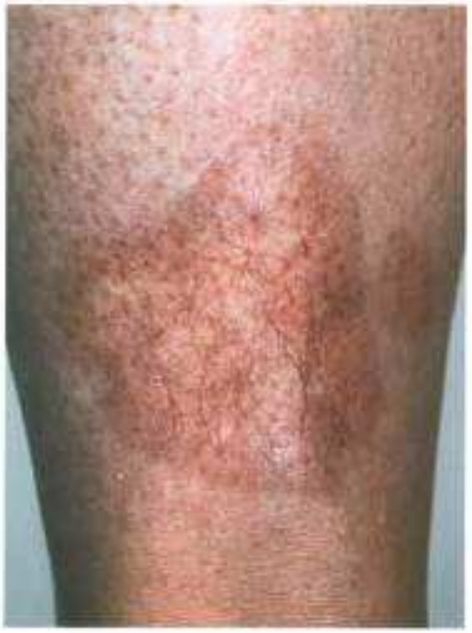


Fig. 1.26 Plaque. A plaque is a raised lesion greater than 1 cm in diameter. The yellow-orange centre and telangiectasia with a mauve edge is typical of *necrobiosis lipoidica*.

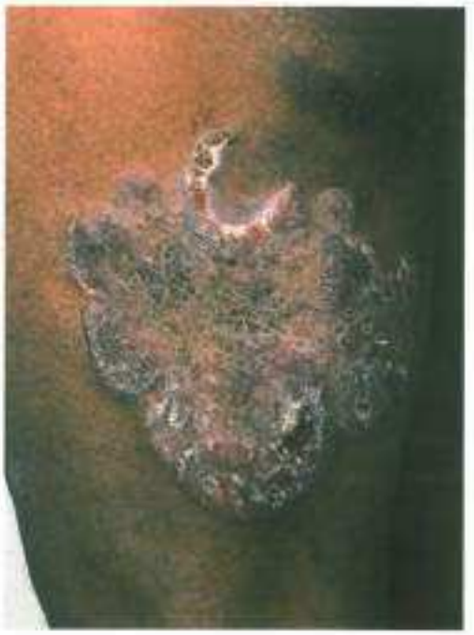


Fig. 1.27 Plaque. This has a well-defined and in some areas indented margin. It is flat in some parts and thickened in others. Biopsy showed it to be *mycosis fungoides*.

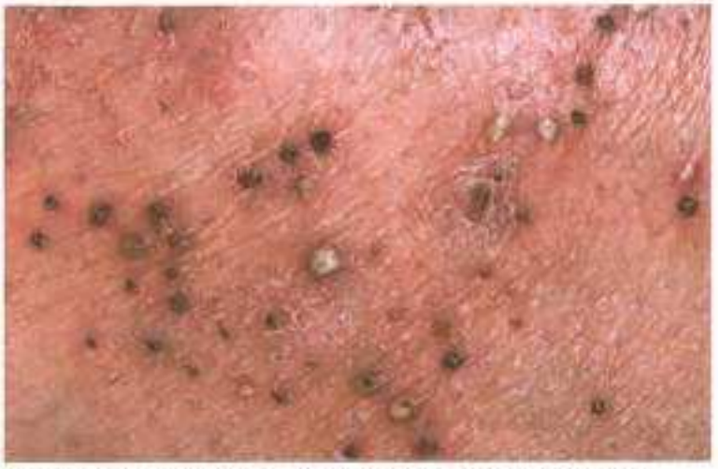


Fig. 1.28 Pustule. A pustule is a raised lesion less than 0.5 cm in diameter containing yellow fluid, which may be infected or sterile. Culture of the pustule in the centre of the picture grew *S. aureus*. This is *folliculitis*.

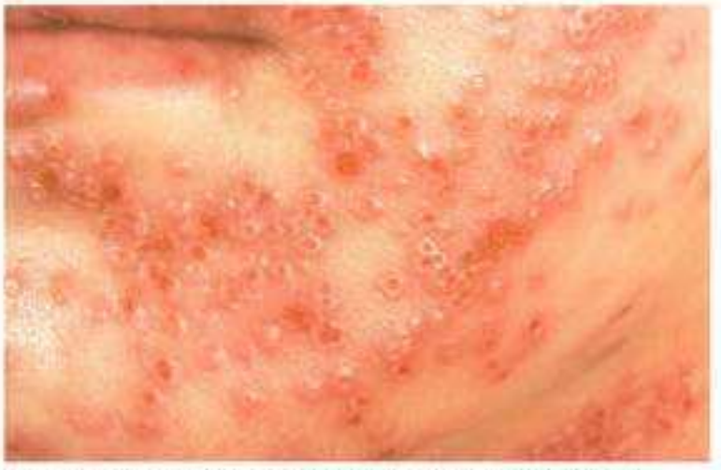


Fig. 1.29 Vesicle. A vesicle is a raised lesion less than 0.5 cm in diameter containing clear fluid. These are umbilicated on the surface. The patient had extensive herpes simplex and eczema (*eczema herpeticum*).

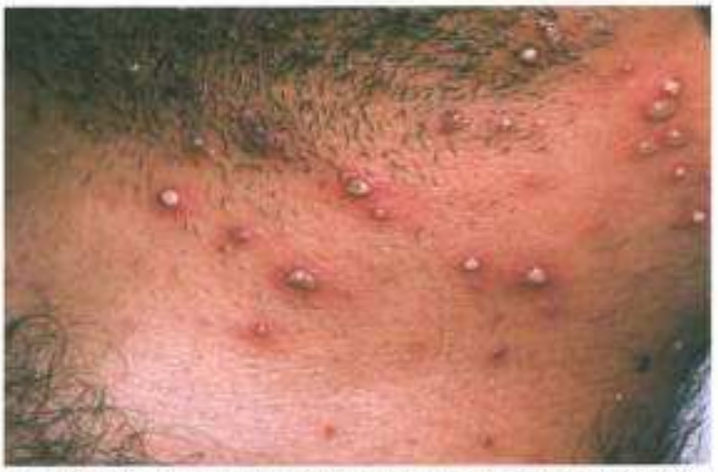


Fig. 1.30 Vesiculopustules. Vesicles initially contain clear fluid but may become turbid or purulent, as in this patient with chickenpox. Note the characteristic erythema around the lesions.

Fig. 1.31 Bullae. A bulla is a vesicle that is greater than 0.5 cm in diameter. Multiple tense fluid-containing blisters are present. Immunofluorescence showed that this child had *bullous lupus erythematosus*.

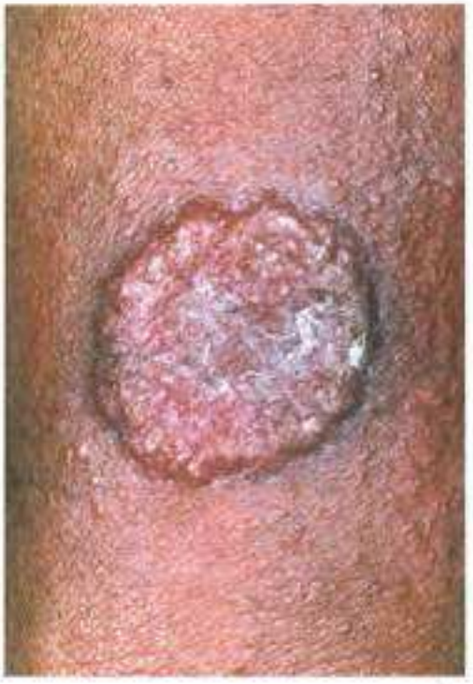


Fig. 1.32 Blistering. Only the edge of this lesion is bullous. The shape is annular and the central area is raised, red and scaling. This was bullous *tinea corporis* caused by *Trichophyton tonsurans*.

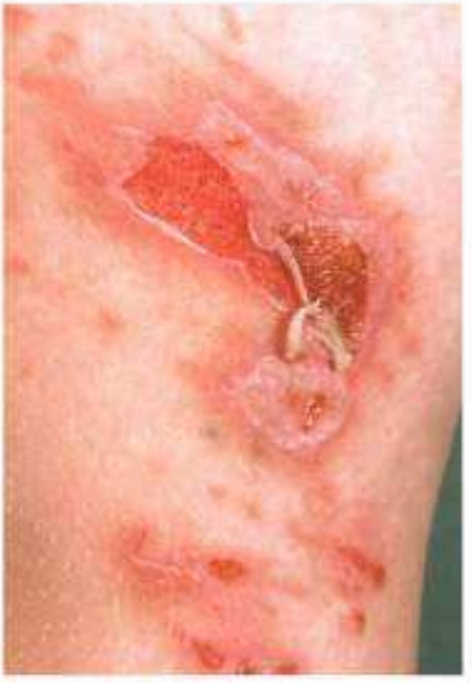


Fig. 1.33 Blistering. The roof of the blisters has been broken in places, resulting in raw, denuded, eroded skin. This linear streaky arrangement was the result of an interaction between a photosensitizer (a psoralen in a plant) and sunlight (*phytophotodermatitis*).

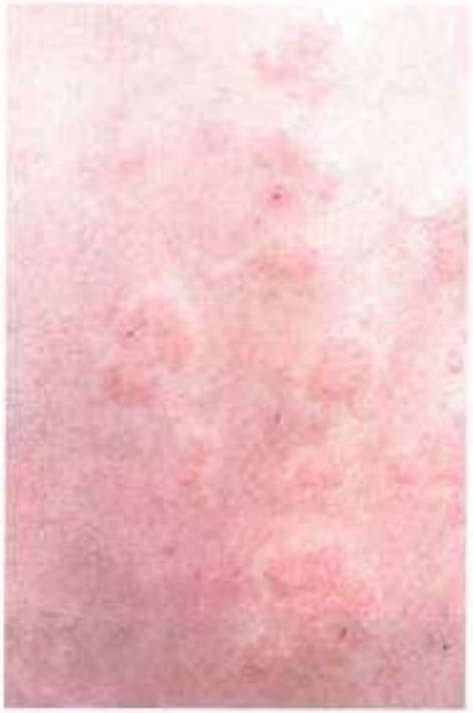


Fig. 1.34 Wheals. A wheal is a transient, itchy, pink swelling that disappears without trace. Wheals often have central swelling of varying size and shape. This patient has *urticaria*.

Fig. 1.35 Wheals. The oedema and varying sizes and shapes of *urticaria* are well shown but the pinkness may be difficult to see in a black skin.

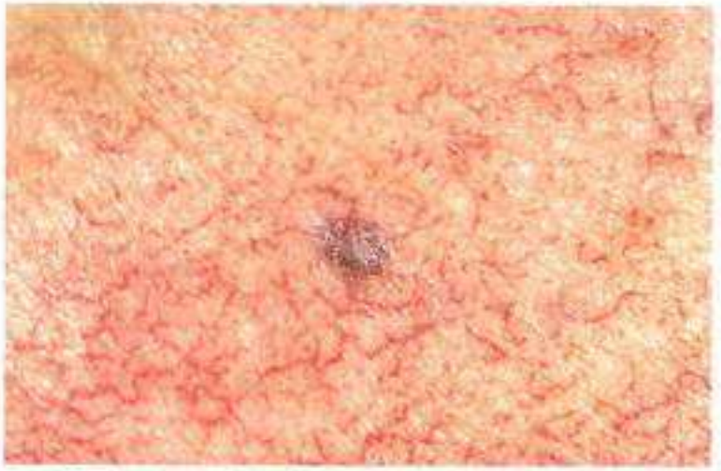


Fig. 1.36 Telangiectasia. A term used to describe finely dilated capillaries. There is also a central red papule (haemangioma). These changes were on the cheeks and were secondary to weathering and *alcohol misuse*.

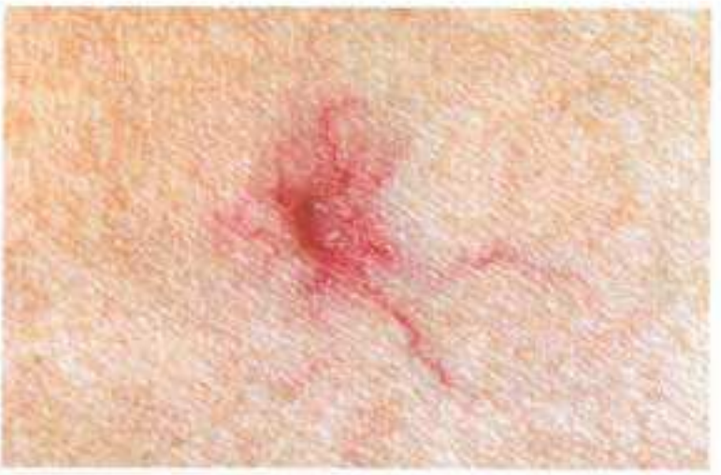


Fig. 1.37 Telangiectasia. These dilated capillaries have spread out from a central red papule, simulating the configuration of a spider, hence its name, *spider naevus*.

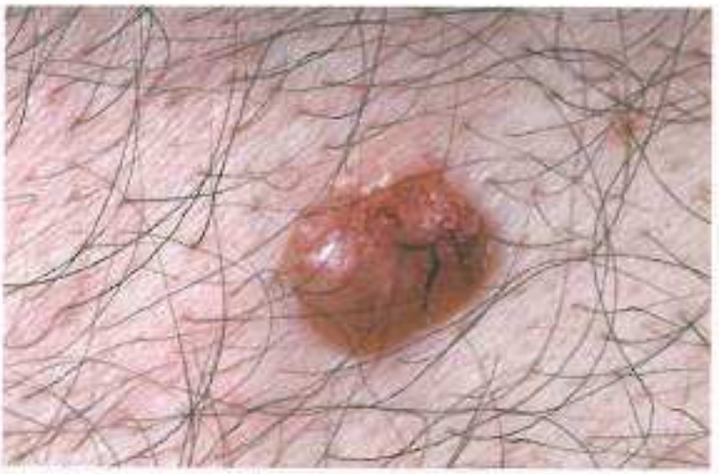


Fig. 1.38 Telangiectasia. This nodule has a pearly colour and a characteristic telangiectatic surface. It is a *cystic basal cell carcinoma*.

Pustule A pustule is a raised lesion less than 0.5 cm in diameter containing yellow fluid, which may be sterile as in acne or pustular psoriasis, or infected (Fig. 1.28).

Vesicle A vesicle is a raised lesion less than 0.5 cm in diameter containing clear fluid (Figs 1.29 and 1.30).

Bulla (blister) A vesicle that is greater than 0.5 cm in diameter is known as a bulla (Fig. 1.31). Insect bites are one of the most common causes of blisters but they also occur in bullous pemphigoid, impetigo, tinea (Fig. 1.32) and phytophotodermatitis (Fig. 1.33).

Wheal A wheal is a transient, itchy, pink or red swelling of the skin, often with central pallor (Fig. 1.34). Wheals can be of various shapes and sizes (Fig. 1.35).

Telangiectasia Visible dilated capillaries (Figs 1.36, 1.37 and 1.38).

Secondary Lesions

Crust A dried exudate, which may have been serous, purulent (Fig. 1.39) or haemorrhagic.

Excoriation A haemorrhagic excavation of the skin resulting from scratching. It may be shallow or deep, linear (Fig. 1.40) or discrete (punctate) (Fig. 1.41).

Lichenification Thickening of the skin with exaggeration of the skin creases (Fig. 1.42).

Lichenoid This term describes lesions that have been scratched and rubbed, giving rise to flat-topped papules similar to those in lichen planus. The appearance is common in eczema in black skins (Fig. 1.43).

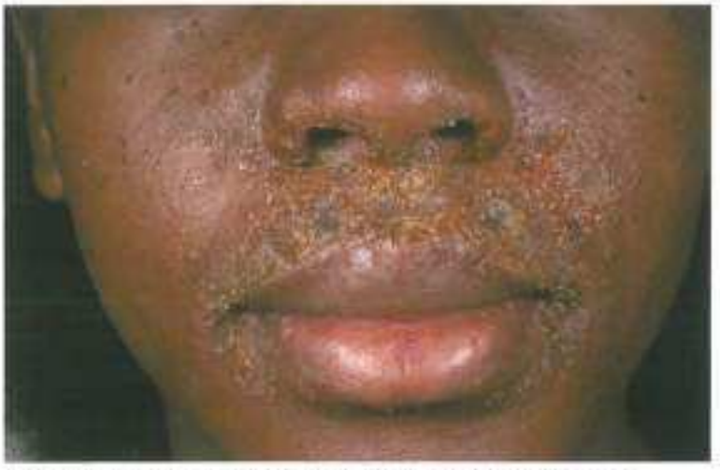


Fig. 1.39 Crust. A crust is a dried exudate, which may have been serous, purulent or haemorrhagic initially. The yellow purulent material visible below the nose has dried in other areas becoming crusted. This is *impetigo*.

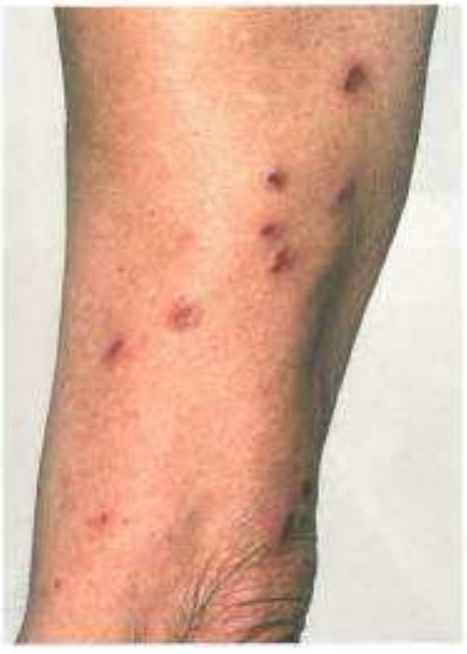


Fig. 1.40 Excoriation. An excoriation is a haemorrhagic excavation resulting from scratching. These discrete scratch marks occurred in a patient who was itching from *primary biliary cirrhosis*.

Fig. 1.41 Excoriation. These haemorrhagic excavations have resulted from interference with the skin. The linear configuration of the lesions is suggestive of *artefactual disease*.

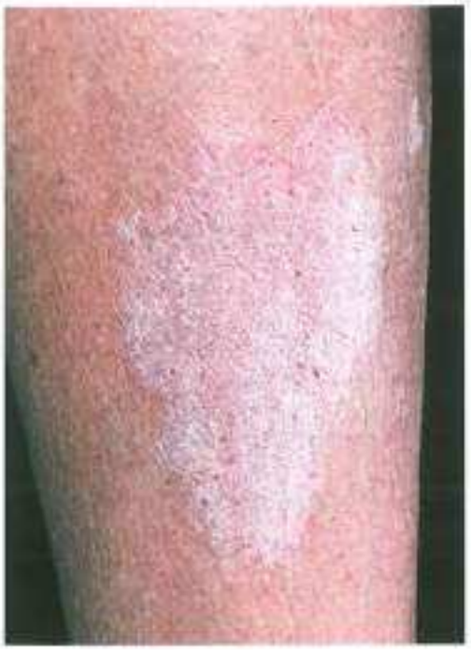


Fig. 1.42 Lichenification. This is a thickening of the skin with exaggeration of the skin creases in a criss-cross manner; it results from continual rubbing and scratching. This is *lichen simplex*.

Fig. 1.43 Lichenoid papules. In black skin in particular, rubbing and scratching of eczematous skin may result in flat-topped itchy papules that simulate lichen planus, hence the term lichenoid.

Necrosis Death, or necrosis, of skin tissue is usually black in colour (Fig. 1.44). Gangrene (Fig. 1.45) is a form of necrosis. Necrolysis is a superficial necrosis with shedding of the skin (Fig. 1.46).

Scar The final stage of healing of a destructive process (disease or injury) that has involved the deeper dermis results in a white, smooth, firm, shiny lesion (Fig. 1.47). There are various forms (Fig. 1.48).

Scaling A scale is a flat plate (lamella) or flake of stratum corneum.

Exfoliation Splitting off of the stratum corneum in fine scales or sheets.

Fissure This is a linear split or gap in the skin surface.

Keratoderma A horny thickening of the keratin layer of the skin. It may occur in a congenital abnormality of keratin formation or as a result of simple mechanical stimulation.

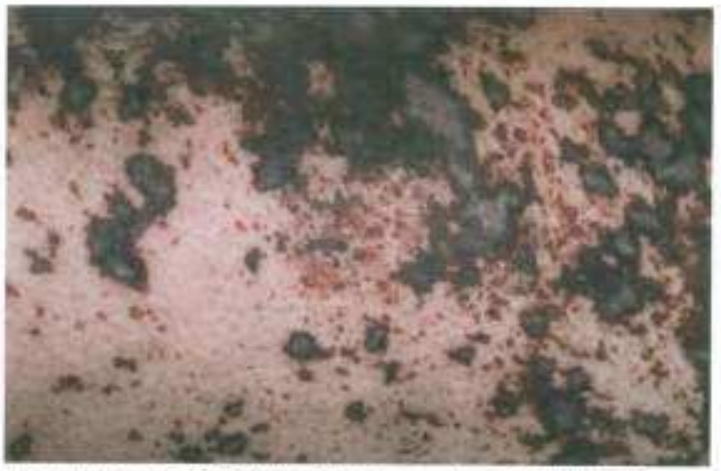


Fig. 1.44 **Necrosis.** This is death of skin tissue and is usually black in colour. These haemorrhagic purpuric lesions are necrotic and are caused by disseminated intravascular coagulation, due to *meningococcal septicaemia*.

Fig. 1.45 **Gangrene.** This is death of skin and other tissue secondary to loss of the blood supply. There is profound necrosis. This patient had *arteriosclerosis* secondary to diabetes mellitus.

Fig. 1.46 **Necrolysis.** There is superficial necrosis and sheeting away of the skin. In this patient with *toxic epidermal necrolysis*, it was particularly marked where the electrocardiograph leads had been applied.

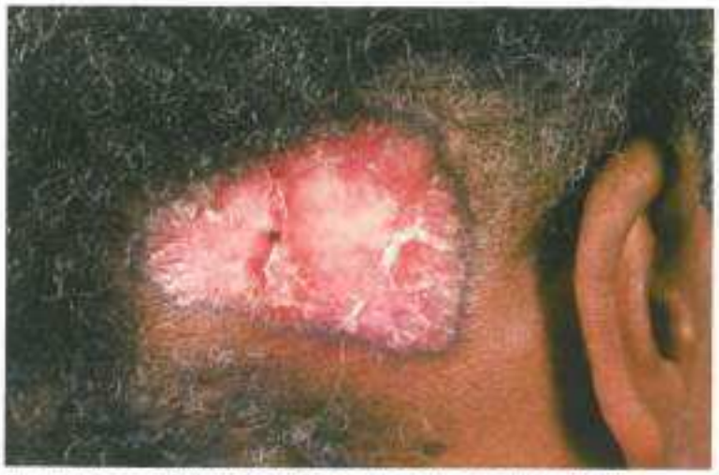


Fig. 1.47 **A scar.** A scar is the final stage of a destructive process that has involved the deeper dermis and resulted in permanent damage to the skin. In this patient with *lupus erythematosus*, hair follicles have been destroyed.

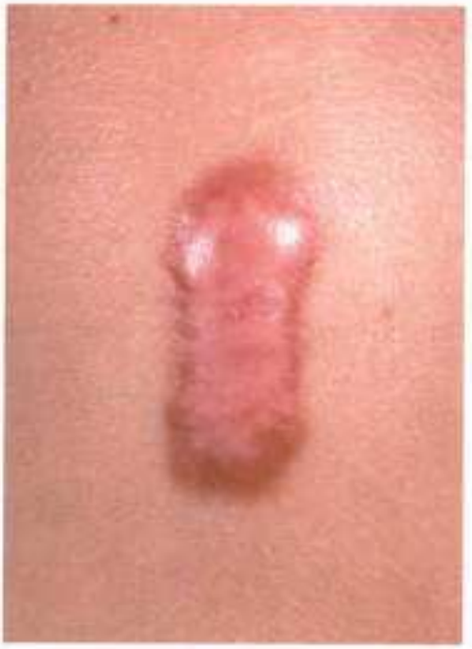


Fig. 1.48 **Keloid scar.** A scar is the replacement of the skin by fibrous tissue. It may be atrophic (thin and wrinkled), hypertrophic or *keloid* (elevated with excess growth of fibrous tissue), or cribriform (perforated with small pits).

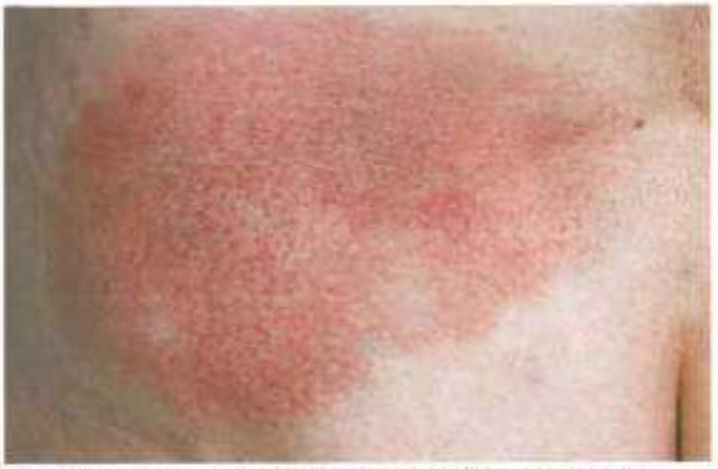


Fig. 1.49 Poikiloderma. This refers to skin that is atrophic, pigmented and telangiectatic. This well-defined patch on the buttock (a characteristic site) was caused by *mycosis fungoides*.

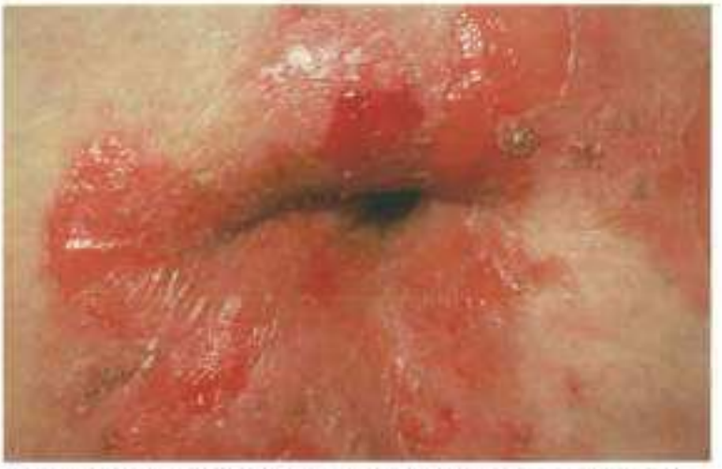


Fig. 1.50 Erosion. An erosion is a partial loss of epithelium, in this case due to intraepidermal blistering, which is visible around the edge of the raw glistening base of the erosions. This is *pemphigus vulgaris* around the umbilicus.

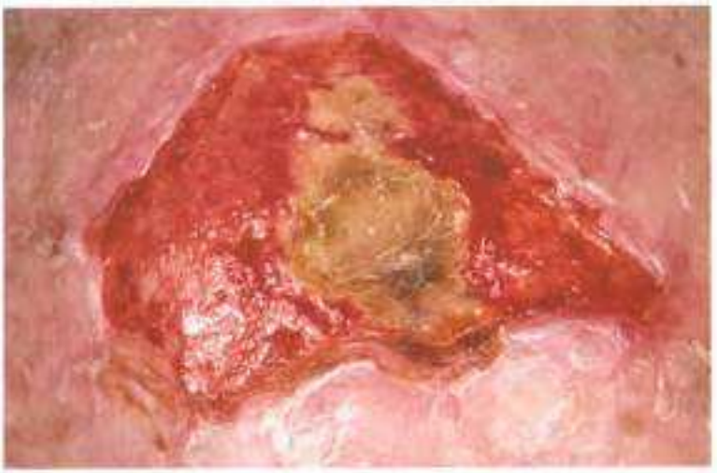


Fig. 1.51 Ulcer. An ulcer is full-thickness destruction of the epidermis. This is *radionecrosis* following irradiation of scalp ringworm.

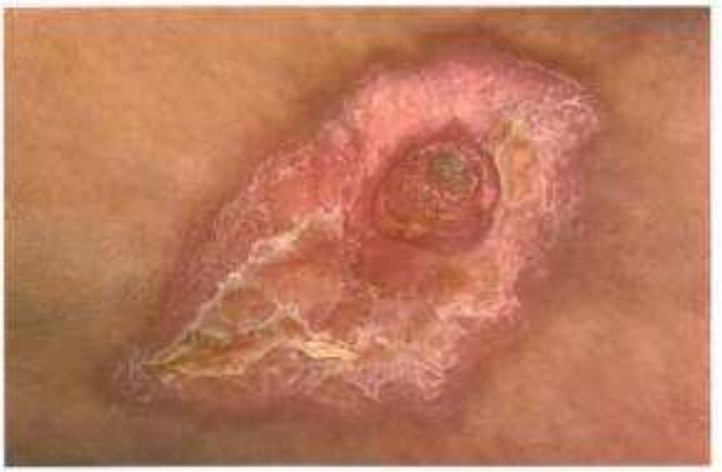


Fig. 1.52 Ulcer. There is an ulcer within a very well-defined, waxy, yellow-red plaque with a mauve edge. This is *necrobiosis lipoidica diabeticorum*.

Poikiloderma This refers to an appearance of pigmentation, atrophy and telangiectasia (Fig. 1.49). The term is derived from the Greek word ποικιλος meaning dappled.

Vegetation A growth of pathological tissue consisting of multiple, close-set, papillomatous masses.

Erosion A partial break in the epidermis is known as an erosion; it heals without scarring unless secondary infection occurs (Fig. 1.50). It commonly follows a blister.

Ulcer An ulcer is a full-thickness loss of the epidermis that heals with scarring (Figs 1.51 and 1.52).

Atrophy Thinning and transparency of the skin is caused by diminution of the epidermis, the dermis, or both (Fig. 1.53). There is wrinkling and translucency of the skin with loss of skin markings.

Sclerosis A circumscribed or diffuse hardening or induration of the skin (Fig. 1.54) can occur as a result of dermal or subcutaneous oedema, cellular infiltration or collagen proliferation.

An eruption may be either essentially monomorphic (e.g. molluscum contagiosum) or polymorphic (consisting of various forms; Fig. 1.55). For example, comedones, papules, pustules, cysts and scars may be found in acne. The lesion may evolve through various stages, such as from macules, to vesicles, pustules and crusts, and sometimes to postinflammatory pigmentation, as in herpes simplex and scarring in chickenpox. Certain other characteristics of the lesions must be observed as described below.

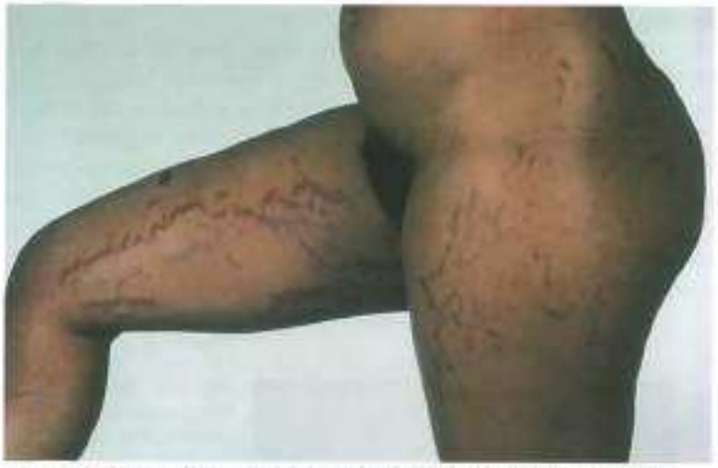


Fig. 1.53 Striae. There is atrophy of both the epidermis and dermis to be seen here on the inner and outer aspects of the thighs secondary to the use of skin lightening creams containing, inter alia, *superpotent steroids*.

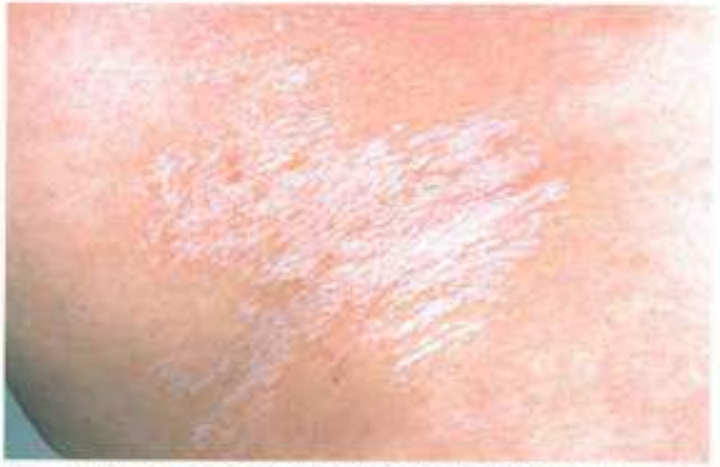


Fig. 1.54 Sclerosis. There is hardening of the skin. Here in *lichen sclerosus et atrophicus*, the ivory-white areas are sclerotic and will become wrinkled and atrophic.

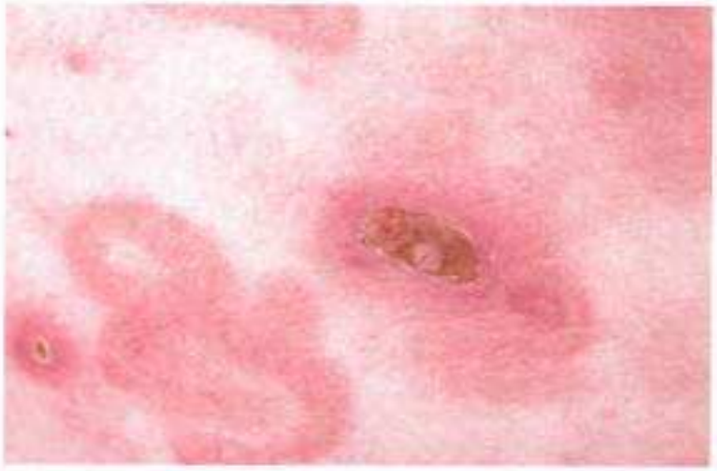


Fig. 1.55 Polymorphic eruption. There are various forms in this patient with *mycosis fungoides*. There is an annular plaque (bottom left), a diffuse pink patch (top right), a necrotic tumour (centre) and a crusted papule (left).

Morphology of the lesions

Once the type or types of lesion have been discerned, they must be defined further in terms of colour, consistency, nature, texture, scaliness or otherwise of the surface, pattern, shape, margin and arrangement.

Colour

The colours found in the skin are derived from melanin (brown), phaeomelanin (as in red hair), carotenoids (yellow), oxyhaemoglobin (bright red) and reduced haemoglobin (bluish red). Their presence, absence, diminution or excess produce a wealth of colours, which are critical for diagnosis of skin disorders. For example, eczema is pink, psoriasis is red and pityriasis versicolor is frequently brown; the papules of lichen planus are purple (Fig. 1.56), of scabies red, of xanthomas yellow (Fig. 1.57) or orange, and of a blue naevus blue. The pigments and colours of a

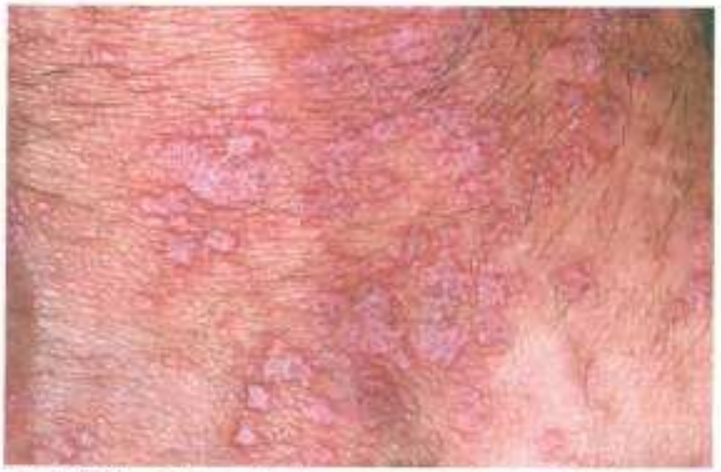


Fig. 1.56 Colour. These papules have merged into each other to form plaques. They have a distinctive purple or violaceous colour with a flat, shiny surface covered with white striae. This is *lichen planus*.

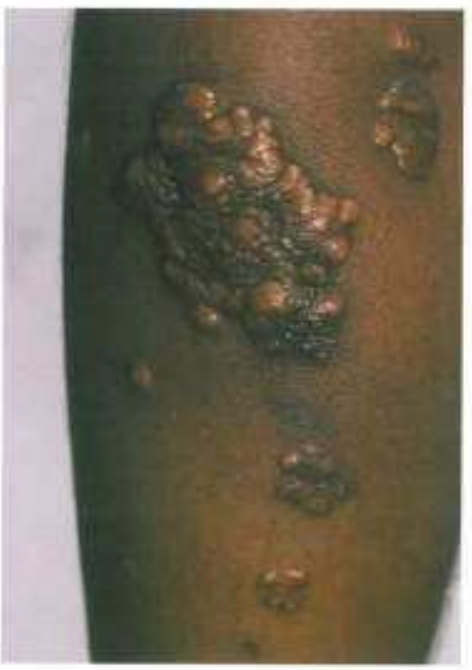


Fig. 1.57 Colour. This may be more difficult to detect in black skin, but even with these papules and nodules a yellow or orange colour is visible amongst the pigment. These xanthomas are secondary to biliary hypoplasia.

superficial spreading malignant melanoma are varied (Fig. 1.58), whereas those of a solar lentigo are quite uniform. Purpura (Fig. 1.59) is distinguished from erythema (see Fig. 1.12) because the latter is red and blanches with pressure, whereas the former is purple and does not. Changes in melanin pigmentation following common inflammatory disorders such as acne and eczema are usual in pigmented races but occur barely, if at all, in white races. This may make diagnosis confusing for the inexperienced as well as bedevil treatment. Certain skin disorders always produce postinflammatory pigmentary changes whatever the patient's basic skin colour (e.g. lichen planus and pityriasis versicolor).

Scale

The skin is shed imperceptibly all the time, since the epidermis is replaced every 28 days. This becomes visible as scales if at least part of the disorder affects the epidermis. In eczema, there is fluid in and around the epidermal cells, producing a disordered epithelium. In psoriasis, the basal cells are mitotically active and a hyperproliferative epidermis results. These disorders are scaly and because they are also red, they are known as erythematosquamous diseases. The scale is fine in eczema and exfoliative dermatitis (Fig. 1.60), and thick and silvery in psoriasis (Fig. 1.61). After sunburn or an infection producing an erythemogenic toxin,

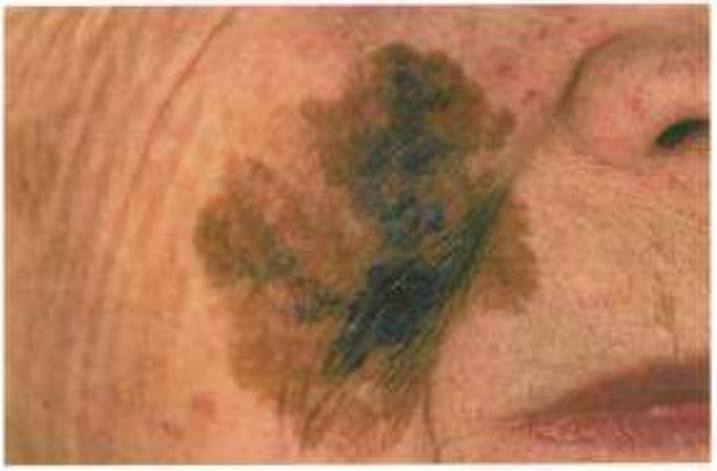


Fig. 1.58 Colour. There is a multiplicity of shades of melanin pigment ranging from light brown to black and an irregular scalloped outline. This is *Hutchinson's lentigo maligna melanoma* on the face.

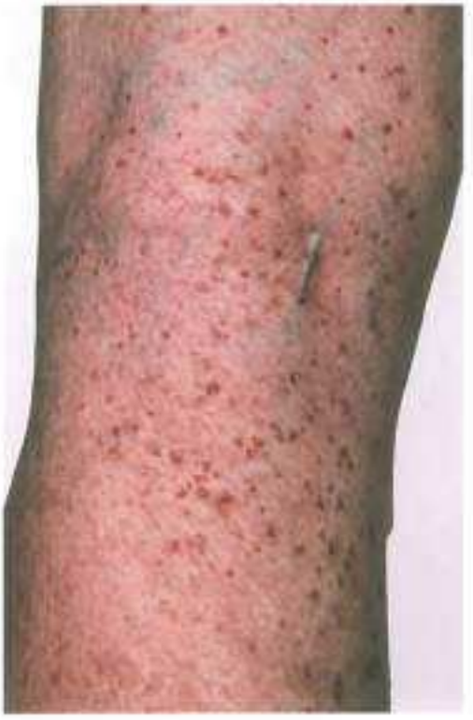


Fig. 1.59 Colour. Purple papules are present. They did not blanch on pressure and this purpuric eruption was confirmed on biopsy to be a vasculitis.

Fig. 1.60 Scale. The scale may be fine as in eczema or as in this case of *exfoliative dermatitis* secondary to the Sézary syndrome.

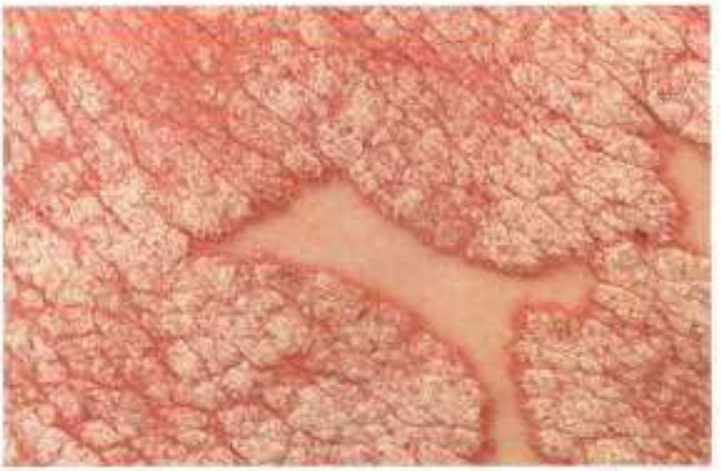


Fig. 1.61 Scale. In psoriasis, the scale is usually thick and a silvery white colour. The lesions are slightly raised plaques and very well defined.

a very superficial peeling of the stratum corneum (desquamation) occurs. In pityriasis versicolor, where there is colonization of the outermost layer of the epidermis by a fungus, the scale may be barely imperceptible until the macules are scraped with a blunt scalpel. The scale may be tenacious, as in lupus erythematosus, or thick and easily scraped off to reveal minute bleeding points, as in psoriasis. The scale may be uniformly spread across the lesion, as in eczema, or more marked peripherally, as in pityriasis rosea. In certain ichthyoses, on the one hand, where there is a failure to desquamate owing to retention of horn cells, scaling occurs without inflammation (Fig. 1.62). On the other hand, if the primary pathology is in the dermis, as in lichen planus or granuloma annulare (Fig. 1.63), no scaling is produced at all.

Shape

Lesions may be round or discoid as in nummular eczema (Fig. 1.64), oval as in pityriasis rosea or all manner of shapes and sizes as in psoriasis. Annular lesions are not synonymous with round ones (Fig. 1.65). The

Fig. 1.62 Scale. In *X-linked ichthyosis vulgaris*, the scale is a flat plate (lamella) and results from steroid sulphatase deficiency such that the corneocytes adhere together incorrectly.

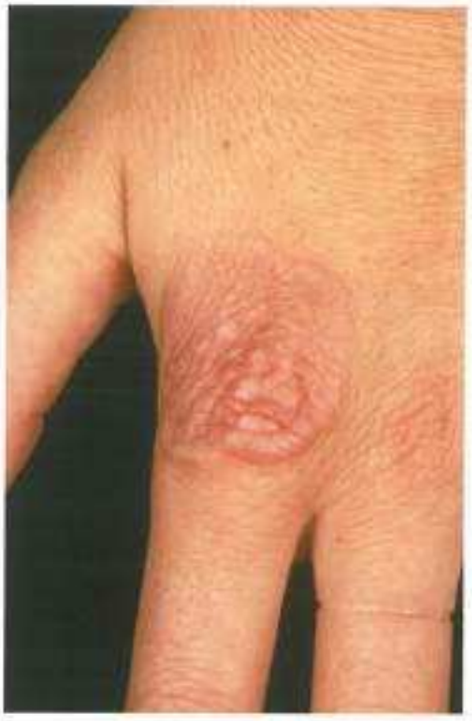


Fig. 1.63 Shape. In *granuloma annulare*, the lesion is annular with a raised margin, often composed of small papules with a contrasting flatter area within. There is no scaling. The back of the hand is a common site.

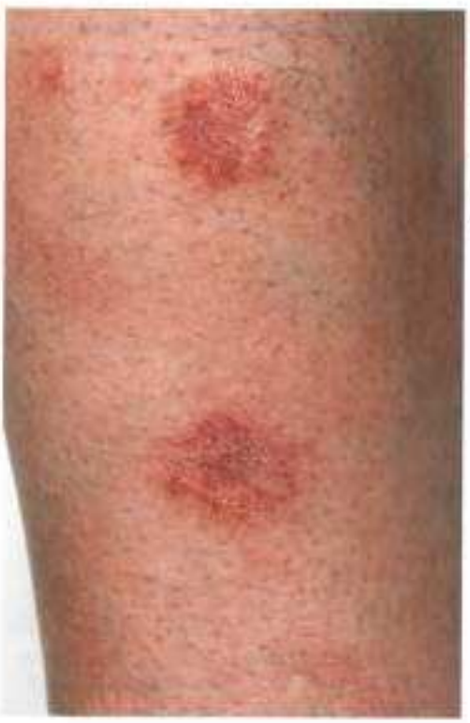


Fig. 1.64 Shape. These lesions are round or discoid in shape. There is no central clearing. The scaling and redness are uniformly distributed. It represents nummular (coin-shaped) or *discoid* eczema.

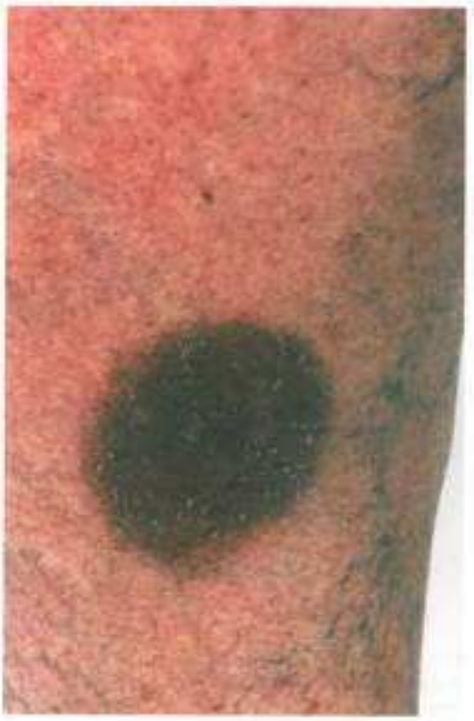


Fig. 1.65 Shape. This completely round pigmented patch is the characteristic appearance of a *fixed drug eruption*.

former have clear or contrasting centres (Fig. 1.66), the latter do not. Polycyclic lesions (Fig. 1.67) are arranged in more than one ring. further distinction can be made on the basis of scaling. Epidermal lesions, such as ringworm (Fig. 1.68) are scaly whereas dermal eruptions, such as sarcoidosis, are not. The individual papules of lichen planus are polygonal in shape.

Surface

The lesion may be rough as in a seborrhoeic wart (Fig. 1.69) or smooth as in dermal melanocytic naevus (a mole). An individual papule may be flat topped, as in lichen planus, pointed (acuminate), as in miliaria rubra, mammilated, as in a compound naevus (Fig. 1.70), or dome shaped and umbilicated, as in molluscum contagiosum.

Consistency

The lesion may be firm as in a dermatofibroma, soft as in a dermal mole, hard as in a secondary deposit or tethered as in scleroderma.

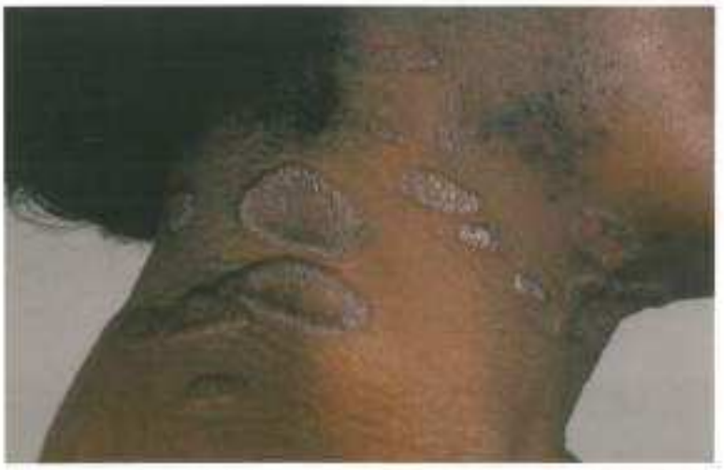


Fig. 1.66 Shape. The lesions are annular or ring shaped with a raised margin and no scaling, indicating that the pathology is not in the epidermis but in the dermis or deeper. This is *sarcoidosis*.

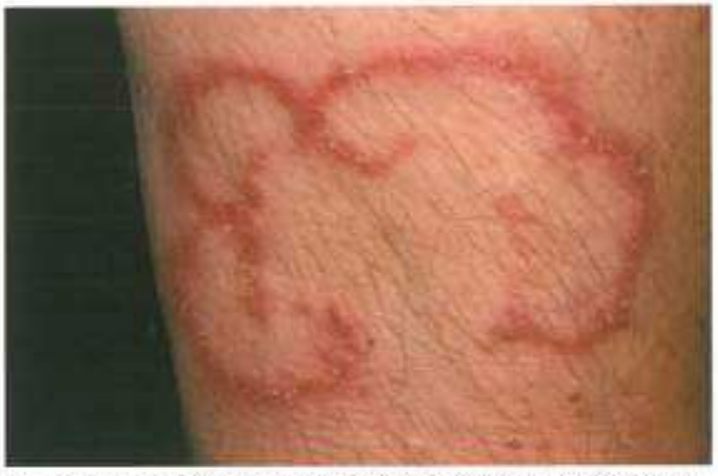


Fig. 1.67 Shape. Polycyclic lesions are arranged in more than one ring. Note the scaling of the slightly raised margin. This is *tinea corporis*.

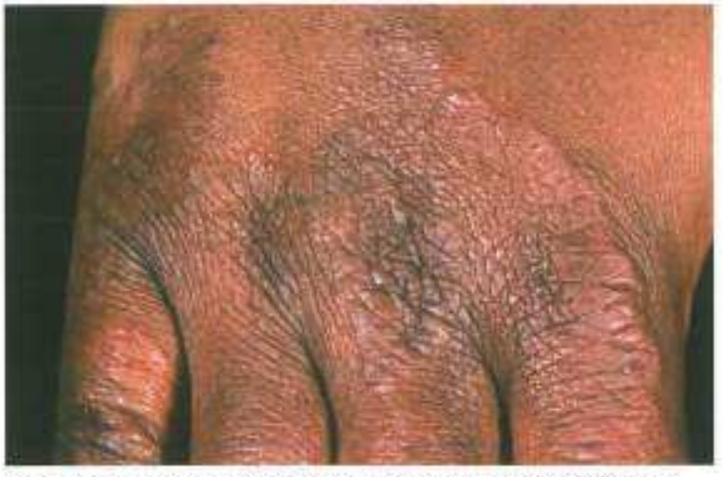


Fig. 1.68 Shape. The eruption is partly annular in outline. The margin is more pronounced and scaly than the pink area within it. Healing has resulted in postinflammatory pigmentation near the fifth knuckle. This is *tinea corporis*.

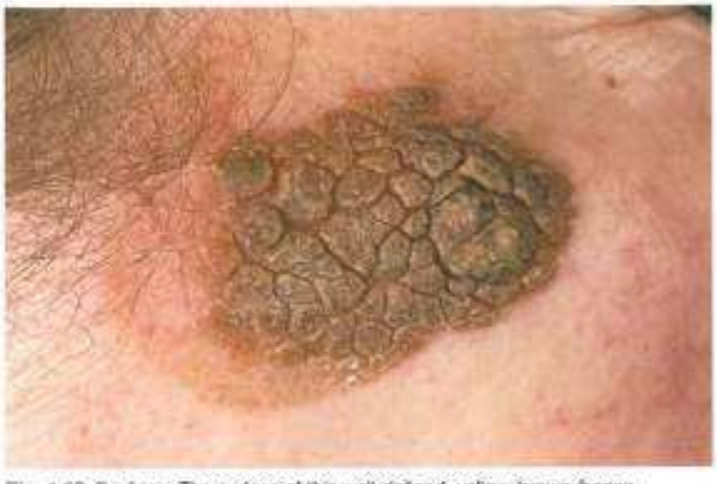


Fig. 1.69 Surface. The surface of this well-defined, yellow-brown (hence seborrhoeic) wart is rough and split (fissured) and appears almost to be stuck to the surface. It is also known as a *basal cell papilloma*.

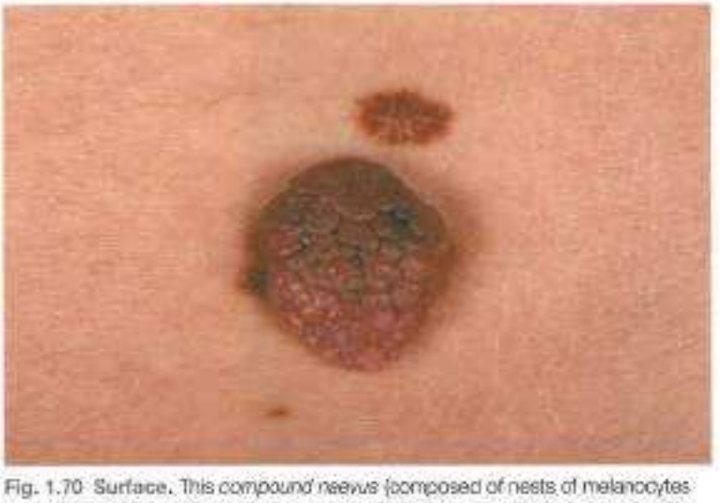


Fig. 1.70 Surface. This *compound naevus* (composed of nests of melanocytes at the dermoepidermal junction and in the dermis) has a mamillated (nipple-like) surface. This benign mole feels soft and the surface is smooth.

Fig. 1.71 Margin. The majority of this annular lesion shows postinflammatory hyperpigmentation but the margin is purple and papular, which is the clue to the diagnosis of *lichen planus*.

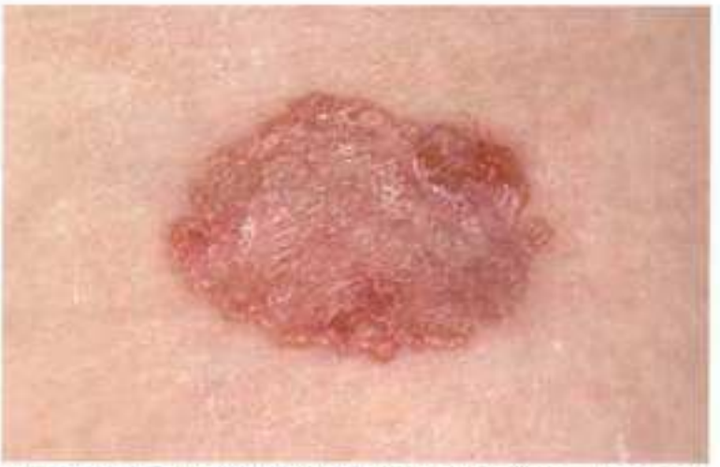


Fig. 1.72 Margin. The border of this well-defined, red, slightly scaly plaque has a distinct rolled pearly edge. It is a *superficial basal cell carcinoma*.

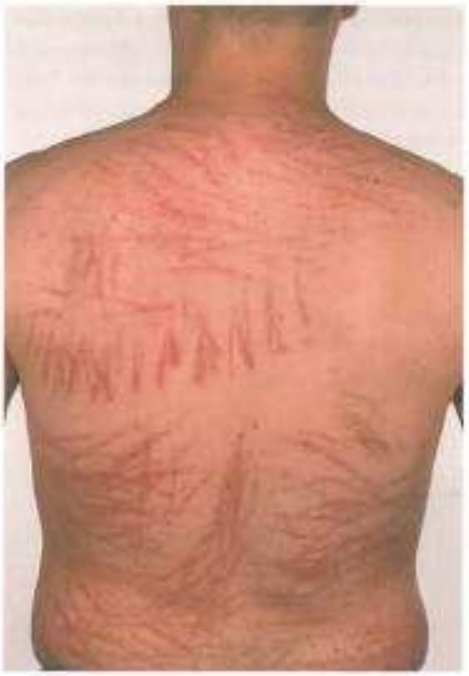


Fig. 1.73 Linearity. This bizarre linear streaky patterned eruption occurred 48 hours after ingesting raw or half-cooked *Shiitake mushrooms* (*Lentinus edodes*). A similar flagellate reaction may occur with bleomycin.

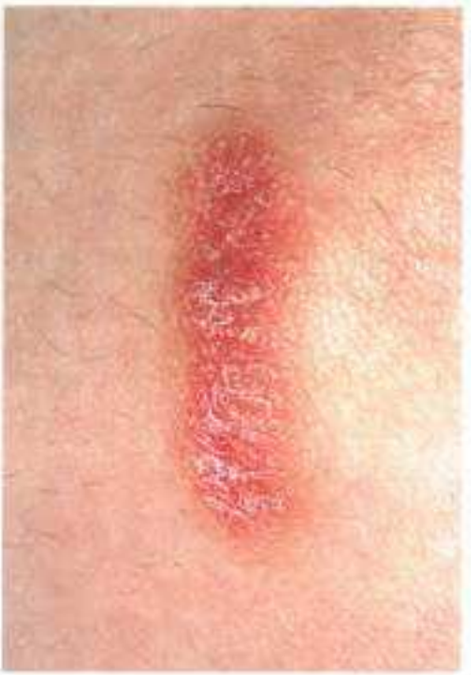


Fig. 1.74 Linearity. This linear deep red lesion with prominent scaling is *psoriasis* occurring in an area of traumatized (in this case scratched) skin. It is known as the *Koebner phenomenon*.

Margin

The lesion may be discrete as in psoriasis or indistinct as in many forms of eczema. There may be more activity peripherally, with a tendency to central healing, as in tinea or annular lichen planus (Fig. 1.71). The margin may be raised and rolled, as in basal cell carcinoma (Fig. 1.72), or irregular and notched as in a malignant melanoma (see Fig. 1.58).

Pattern

The lesions may be arranged in a particular manner. They may be linear, annular, grouped or reticulate.

Linear pattern

Linearity may be explained by involvement of a dermatome (e.g. herpes zoster), of blood vessels (e.g. thrombophlebitis) or of lymphatics (e.g. sporotrichosis or lymphangitis). Exogenous agents such as plant allergens or their derivatives produce linear streaking (e.g. phytophotodermatitis and poison ivy dermatitis) and pigmentation (e.g. Berloque dermatitis) on exposed skin. Drugs, especially bleomycin and shiitake mushrooms (Fig. 1.73) may produce bizarre flagellate-like streaking patterns on the skin. Some self-induced lesions such as artefacts are linear in arrangement.

Linear lesions may be of developmental origin (e.g. epidermal naevi) or may follow Blaschko's lines, which do not conform to any known vascular or nervous structure. Other lesions may be determined by the Koebner (or isomorphic) phenomenon (Fig. 1.74), which is the induction of an eruption at the site of trauma, be it scratching or ultraviolet light. Certain diseases manifest this phenomenon (e.g. psoriasis, lichen planus and plane warts). However, there are many linear configurations that are unexplained (e.g. lichen striatus, lichen sclerosus, linear morphoea and porokeratosis of Mibelli). Finger-like shapes are typical of digitate dermatosis (Fig. 1.75).

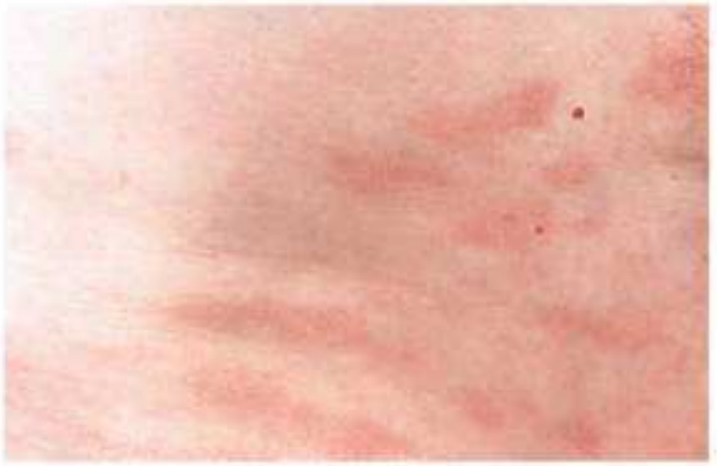


Fig. 1.75 Linearity. These finger-like processes are a distinctive part of *digitate dermatosis* (chronic superficial scaly dermatosis), a probable aborted form of mycosis fungoides.

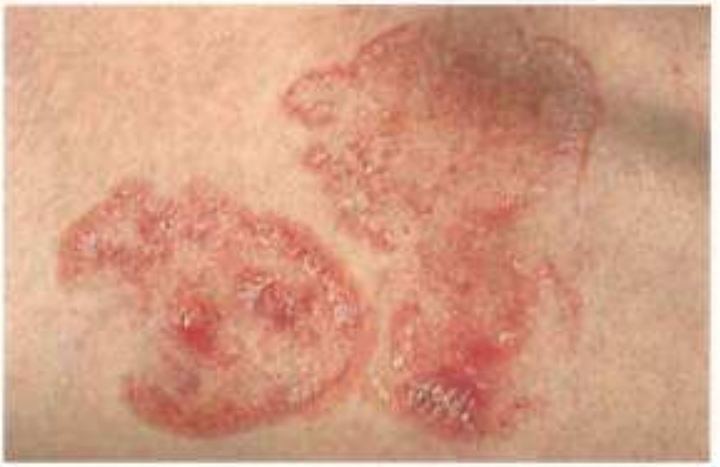


Fig. 1.76 Arciform and polycyclic lesions. The red, scaly plaque on the left is arciform (an incomplete circle) and on the right is polycyclic. Biopsy confirmed *mycosis fungoides*.

Annular pattern

Annular, arciform (incomplete circular lesions; Fig. 1.76) and polycyclic forms are common. They have to be defined further as to whether they are macular (e.g. annular erythema), papular (e.g. granuloma annulare), scaling (e.g. tinea corporis) or nodular (e.g. sarcoidosis, tertiary syphilis or mycosis fungoides). A special configuration is the iris or target lesion (Fig. 1.77), which is almost unique to erythema multiforme.

Grouped lesions

If lesions occur in a group and make a particular pattern, a diagnosis may sometimes be readily obtained (e.g. insect bites). The cluster of vesicles in herpes simplex (Fig. 1.78) is so characteristic that the term herpetiform is used to describe other conditions that simulate grouped vesicles (e.g. dermatitis herpetiformis). Similarly, the linear pattern of vesicles in groups seen in herpes zoster lends the title zosteriform to certain eruptions that occur in a band-like manner (though not conforming to a dermatome) and, in particular, to naevoid conditions. Another rather old-fashioned term that is sometimes used is corymbiform. This means a central cluster of lesions beyond which are scattered individual lesions, a phenomenon that is sometimes seen in verrucae.

Reticular arrangements

A net-like (Latin *reticulum* means a little net) arrangement is seen in particular in livedo reticularis (Fig. 1.79), cutis marmorata and erythema ab igne, where the horizontal pattern of blood vessels under the skin is highlighted. Lichen planus produces just such a pattern in the mouth (Fig. 1.80). The individual papule of this disease may be seen to have a white lace-like change in its surface (Wickham's striae).

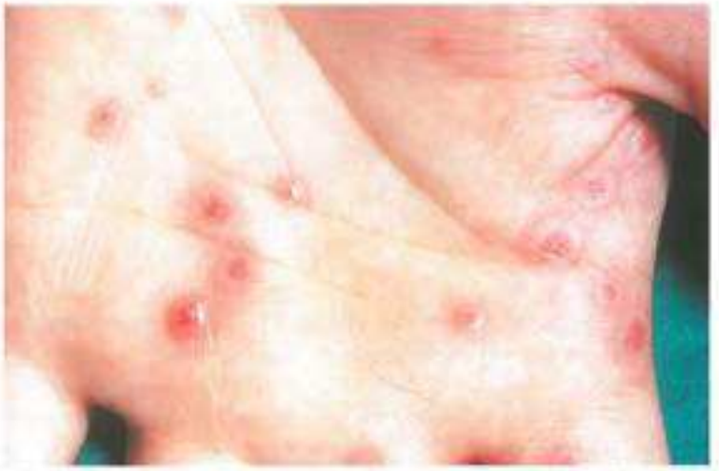


Fig. 1.77 Target lesion. These plaques with a target or iris annular configuration are virtually diagnostic for *erythema multiforme* caused by herpes simplex.

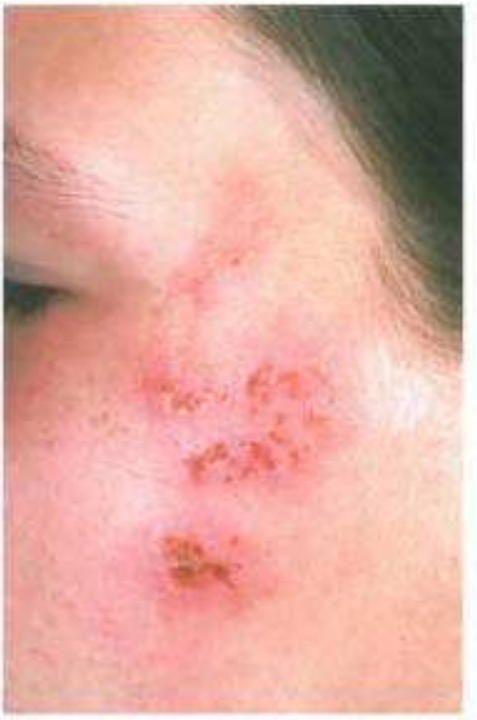


Fig. 1.78 Grouped lesions. These vesiculopustular lesions are grouped together on an erythematous background. This is *herpes simplex*; such an arrangement in other conditions is often known as herpetiform.

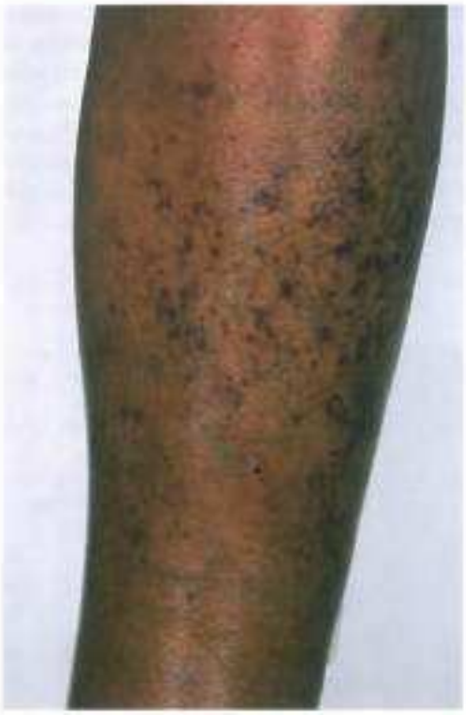


Fig. 1.79 Reticulate pattern. A pattern of pigmented lines presents in a net-like configuration where the horizontal plexus of blood vessels under the skin has been highlighted and is known as *livedo reticularis*. This woman had cryoglobulins secondary to hepatitis C causing vasculitis.

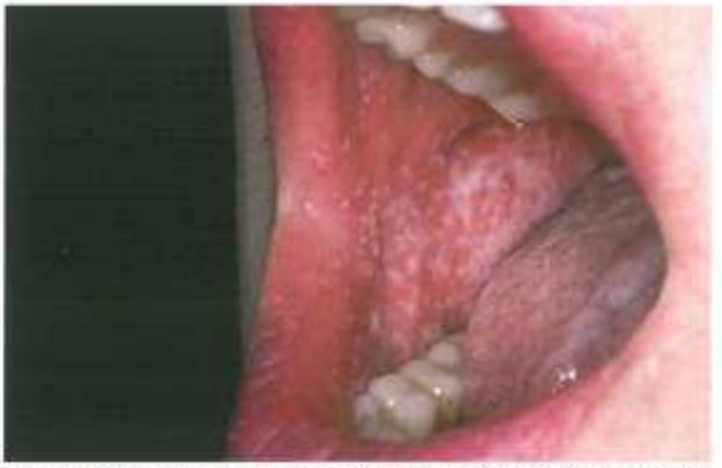


Fig. 1.80 Reticulate pattern. A characteristic net-like (reticulate), white patterning occurs in the mouth, particularly on the buccal mucosa, in *lichen planus*.

Distribution of the lesions

The importance of the morphology of the skin lesions has been emphasized. Consideration of the distribution of these lesions is the next critical step in diagnosis. The diagnosis often can be made based on the distribution. Papules on the genitalia (Fig. 1.81) are virtually diagnostic of scabies in someone who is itching.

Lesions may be localized (e.g. herpes simplex), regional (e.g. acne vulgaris), generalized (e.g. severe psoriasis) or universal (i.e. involving the whole skin, hair and nails, e.g. erythroderma; Fig. 1.82). The favoured habitat of an eruption may be explicable and, therefore, logical, or it may be quite unexplained at present and, consequently, the information must

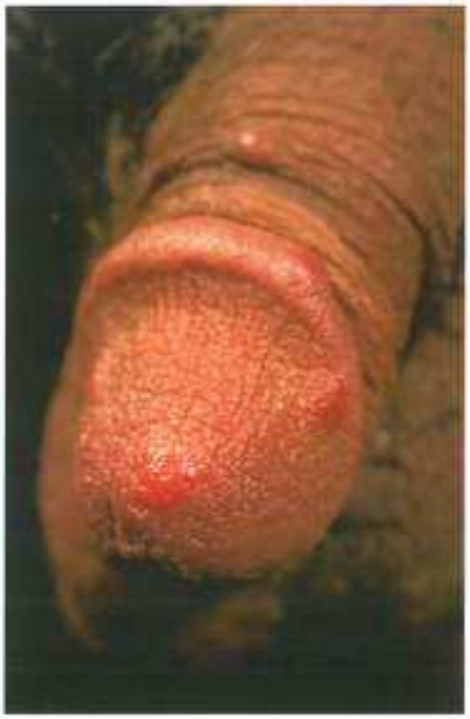


Fig. 1.81 Distribution. In *scabies*, the finger webs, palms and soles are favoured sites for the acarus mite to burrow. Red papules on the glans penis and scrotum are virtually diagnostic.

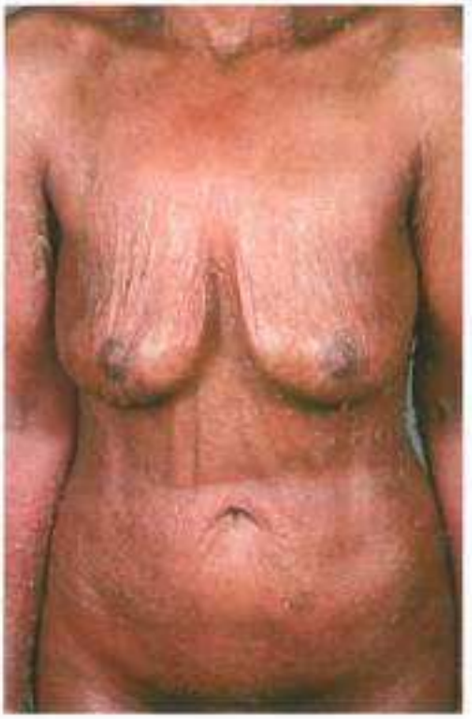


Fig. 1.82 Distribution. The whole of the integument is involved in erythroderma. This patient had the *Sézary syndrome*.

just be committed to memory. The distribution of a skin disorder may be explained by:

- **Innoculation** For example, primary chancre or herpes simplex on the genitalia or elsewhere.
- **Exposure** For example, to a chemical (e.g. contact dermatitis to metal earrings), ultraviolet light (e.g. porphyria, lupus erythematosus (Fig. 1.83) or a phototoxin) or trauma (e.g. callosities (Fig. 1.84) or epidermolysis bullosa).
- **The anatomy of the skin** Acne vulgaris is a disorder of the pilosebaceous glands and appears in the distribution of those glands. If minor acne around the chin is misdiagnosed as eczema and treated with topical steroids, a condition called perioral dermatitis (Fig. 1.85) results. The superficial fungus that causes pityriasis versicolor is lipophilic and is dependent upon active sebaceous glands; consequently, it usually occurs after puberty and predominantly on the trunk (Fig. 1.86) where the sebaceous glands are most active. Hyperhidrosis affects those areas

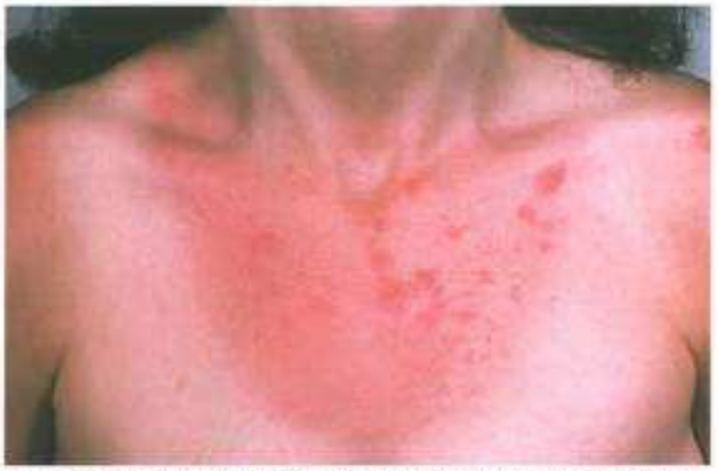


Fig. 1.83 Distribution. Certain dermatoses are aggravated or precipitated by ultraviolet light. Note the red plaques, which have arisen in a sunburnt area of the V of the front of the chest. This is *lupus erythematosus*.

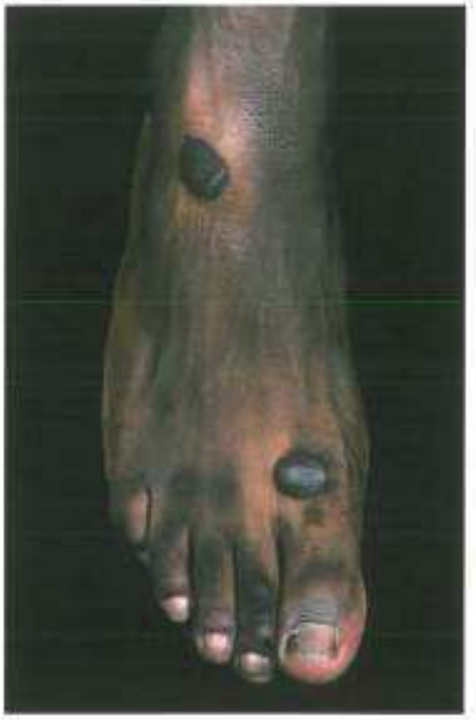


Fig. 1.84 Distribution. These localized areas of hyperkeratosis are callosities secondary to friction, which has stimulated epidermal cell hyperproliferation. They are *prayer nodules*.

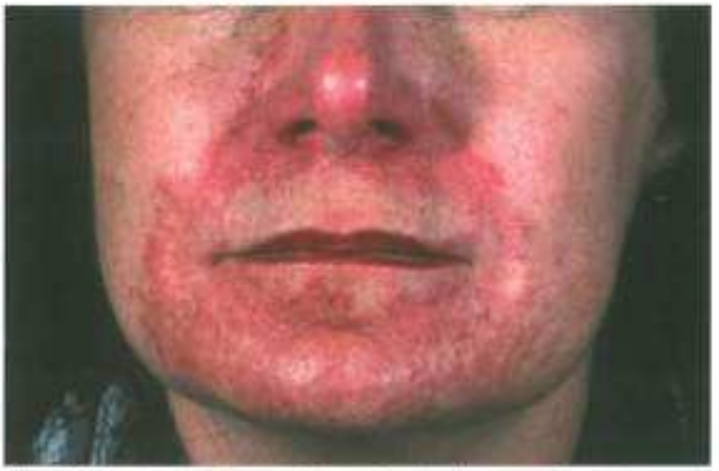


Fig. 1.85 Distribution. There are itchy confluent red papules and pustules around the mouth. It was misdiagnosed as eczema and treated erroneously with powerful topical steroids. This is *perioral dermatitis*.

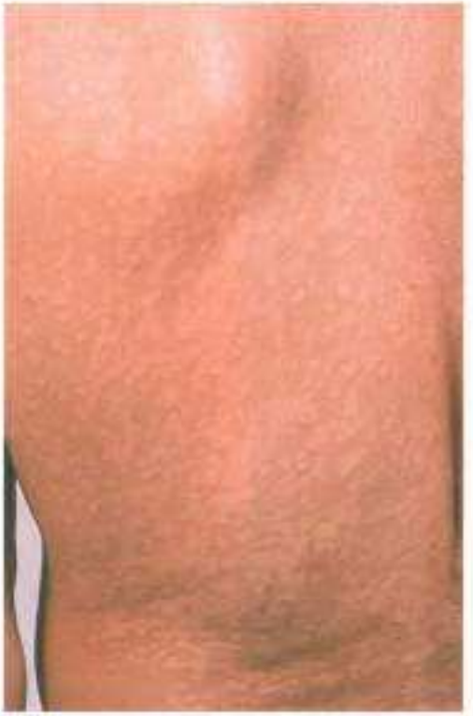


Fig. 1.86 Distribution. The *Pityrosporum* yeast responsible for *pityriasis versicolor* is lipophilic. It favours the trunk where sebaceous glands are most active.

where the eccrine sweat glands are most numerous. Certain disorders, such as keratosis pilaris, vitamin A deficiency and folliculitis, affect the follicular apparatus. Others, such as circulatory disorders, affect blood vessels. The disorder of rosacea is partially explicable by the involvement of the blush area of the face. Herpes zoster is a viral infection usually involving a single cutaneous nerve; therefore, the eruption is unilateral and corresponds to the dermatome affected (Fig. 1.87). The finding of vesicles surrounded by erythema confirms this diagnosis.

Regional variations in the anatomy of the skin may be important. The thick horny layer of the palms and soles is particularly suitable for the scabies mite to burrow into. Areas of increased moisture and temperature are suitable habitats for fungi, and so *Candida albicans*, particularly, favours intertriginous areas and the mouth. Hair and nails are dead structures and are fairly easily colonized by dermatophytes.

The eruption may be bilateral and symmetrical, often suggesting an endogenous aetiology, as in allergic vasculitis, or it may be asymmetrical and unilateral (Fig. 1.88) owing to an external cause. Frequently, however, the distribution of eruptions is not yet explicable. For example, psoriasis principally affects the scalp, elbows, knees and buttocks. Lichen planus has a predilection for the fronts of the wrists, ankles, umbilicus, lumbar area, genitalia and oral mucosa but their distribution is not understood.

Summary

In the study of dermatology, one is exposed to a constellation of signs that have to be evaluated in order to produce a diagnosis. Eczema, for example, may consist of dry, pink patches with scales and fissures or vesicles that weep and crust; all of which may become excoriated, lichenified, pigmented and secondarily infected. Such a condition is difficult to visualize from a cold description in a text book. It needs to be seen frequently to be understood. So, although colour photography has greatly enhanced the teaching of skin disorders, it is very important to watch, to listen and to learn from a specialist at work in the clinic. Subsequently, one can explore for oneself, but hopefully with the chief not too far away, regularly peering over one's shoulder, checking the diagnosis and questioning how it has been arrived at.

Tools of the trade

Dermatology is one of the last bastions of clinical medicine, and 'high-tech' – although undoubtedly now a feature – is unnecessary most of the time. Dermatologists probably request fewer laboratory tests than many specialists in other disciplines. However, a dermatologist does need certain equipment.

An ordinary microscope This is used for the examination of skin scrapings fixed in potash for fungi and for the identification of the acarus, nits and pediculi.

Various basic surgical instruments These include a curette, scissors, needle holder, forceps and scalpel. Curettage of warts and pyogenic granuloma and excision of dermatofibroma and benign moles are all procedures that any medical practitioner can perform, provided that the specimens are sent for histological examination. The various surgical techniques are better demonstrated in operating theatres than described here. Diagnostic incisional or punch skin biopsy is best performed by the dermatologist, as the choice of which part of a skin eruption to biopsy requires experience to obtain a satisfactory pathological specimen. It may also be useful to process the specimen for immunofluorescence, electron microscopy, cell markers or microbiology in addition to routine pathology. Malignant tumours should be referred because their management is often complicated.

A cautery machine This is essential for simple minor surgical procedures such as cautery of skin tags and spider naevi or after a curettage.

A Wood's light This ultraviolet lamp has a nickel oxide (Wood's) filter that excludes visible ultraviolet and emits radiation with a wavelength of 360 nm. This is a useful diagnostic tool; under its rays, erythrasma, a corynebacterial infection of the skin, fluoresces a coral-pink colour, certain ringworm infections of the scalp hairs fluoresce green and pityriasis versicolor fluoresces a yellow colour. Other disorders that fluoresce include porphyria cutanea tarda (urine and faeces), erythropoietic porphyria (teeth), protoporphyria (blood) and tetracycline deposition (teeth and sebum). Pigmentary disorders affecting the epidermis may be highlighted. The ash leaf hypopigmented macule of tuberous sclerosis becomes more apparent and the pigmentary abnormality of pityriasis versicolor is more obvious under the Wood's light.

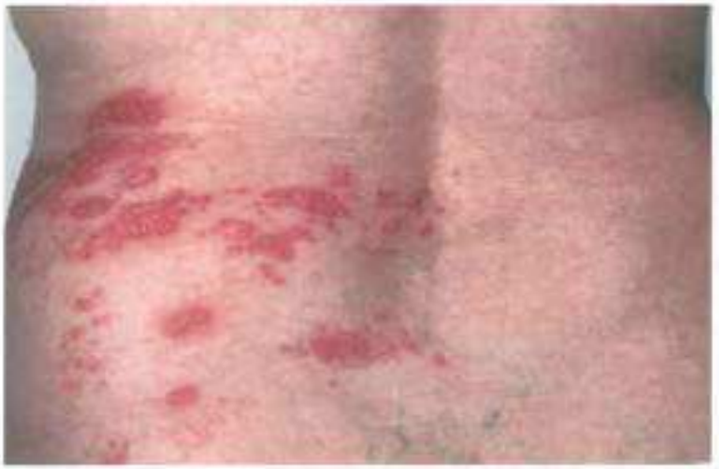


Fig. 1.87 Distribution. The eruption of *herpes zoster* is unilateral in the distribution of a cutaneous nerve. It is painful and vesicles surrounded by erythema dominate the early stages.

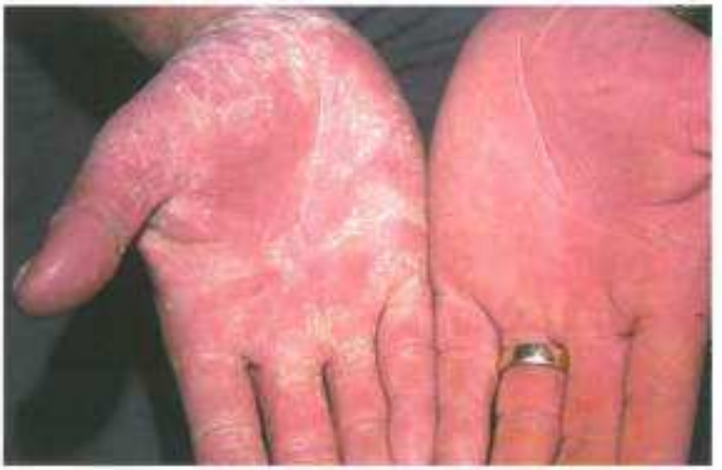


Fig. 1.88 Distribution. Asymmetry is an important clue to diagnosis. Only one palm is involved in this patient with a *Trichophyton rubrum* (fungus) infection and this is characteristic.

A dermatoscope This hand-held instrument magnifies, and enhances with a light source, the visual image of a lesion. It may be helpful in differentiating a malignant melanoma from a benign mole, seborrhoeic wart or haemangioma. It has become a specialized and skilled technique which is increasingly being used, but if there is any doubt about the nature of a mole, it is wisest to take it out. It is also useful for demonstrating an acarus in a burrow.

The dermatologist and colleagues

The family practitioner is the closest associate. It is extremely helpful if the skin department has a 'hot line' so that arrangements can easily be made for acute eruptions, distressed patients and suspicious, pigmented moles to be seen immediately.

In the hospital, the dermatologist is a frequent visitor to every ward, usually because of drug eruptions, and, therefore, comes into contact with all specialists. Some specialities have a particularly close liaison with the dermatologist. For example, pathologists and dermatologists need to meet routinely to review the previous week's dermatopathology, as it is difficult for either speciality to work constructively without regular dialogue. Most pathology departments also have facilities for immunofluorescence, which is now an essential investigative technique in the diagnosis of disorders such as bullous pemphigoid and dermatitis herpetiformis.

Although most dermatologists look at their own skin specimens for the diagnosis of fungal disorders, the microbiology department is indispensable for culturing specimens. The microbiologist is also an important colleague as he or she can give advice regarding appropriate antimicrobial therapy in patients with infective or infected skin diseases. The virologist is particularly required for the diagnosis of serious disorders such as primary herpes simplex, Kaposi's varicelliform eruption, generalized herpes zoster and, formerly, smallpox.

Most dermatologists work closely with a plastic surgeon and a radiotherapist and have combined clinics for the management of malignant diseases of the skin. A liaison with a good general physician is very helpful with regard to the sick patient, for it is a rare dermatologist who can keep up with all the developments in general medicine when matters are proceeding so quickly in dermatology itself. A liaison psychiatrist in the skin department is invaluable. A significant number of dermatological patients have affective disorders and whereas they might be unwilling to see a psychiatrist in a department of psychological medicine, they find the venue of the skin department acceptable. Paramedical staff are essential. Many nurses regrettably go through their training with little or no exposure to the management of skin diseases. As a result, they may be puzzled by the presence of a healthy person with severe eczema or psoriasis in a hospital bed and have no understanding of how to care for the skin in a serious condition such as toxic epidermal necrolysis. Nonetheless, the nurse who understands the use of dithranol in psoriasis and topical corticosteroids in eczema, the applications of dressings and the treatment of leg ulcers is invaluable in a day-care and inpatient setting. Many are now trained to supervise and administer narrow-band and PUVA therapy and also conduct patch tests.

Although dietary measures have only been proven to be highly effective in the management of dermatitis herpetiformis (with the elimination of gluten), dietitians are very helpful in the management of small children with eczema (where the elimination of dairy products can be hazardous) and of urticaria.

The photographic department is important for recording lesions, and for monitoring progress in treatment. Teledermatology may be an adjunct to diagnosis when access to a dermatologist is difficult, but otherwise, in my view, is fraught with difficulties. The skin cannot be examined thoroughly (essential for diagnosis and for patient satisfaction), the lesions cannot be palpated and the visual image will always be inferior to that seen with the naked eye. By the same token, patients often bring photographs of their condition captured on a mobile phone, but the quality of these images varies.

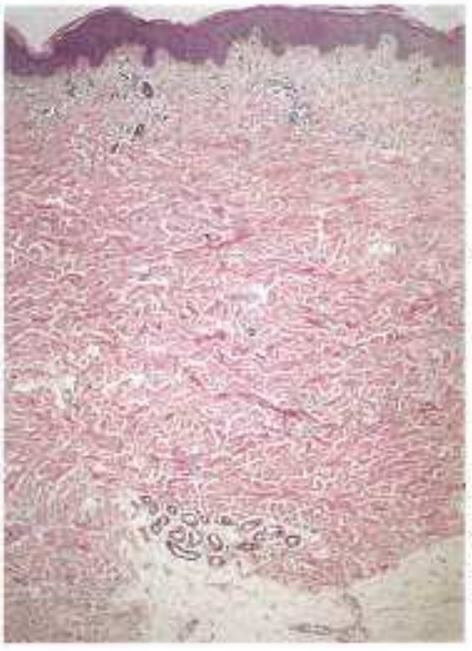
Finally, most skin departments have the help of a cosmetic expert to teach patients how to disguise disfiguring disorders such as port-wine stains.

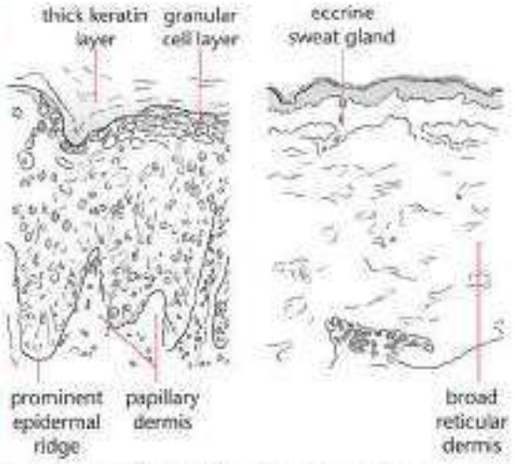
The structure and function of normal skin

2

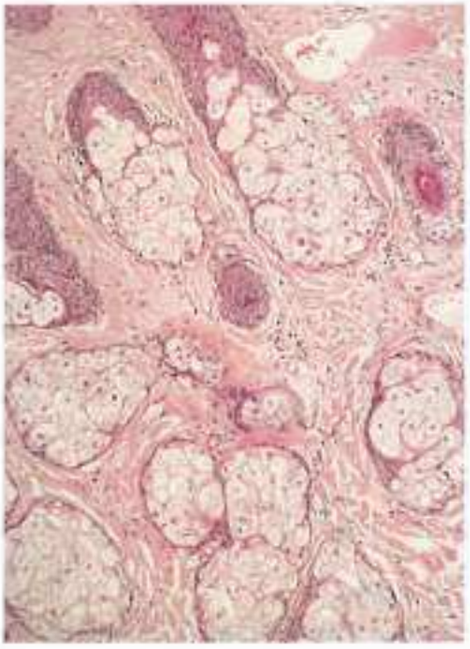
Introduction to skin structure

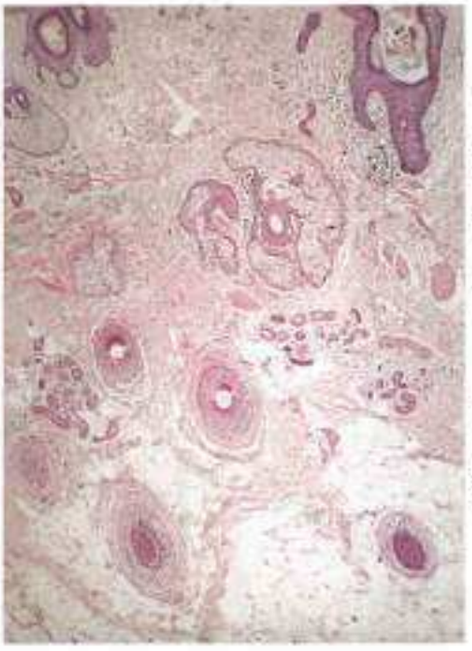
The skin is composed of an outer epithelial layer called the epidermis and an underlying connective tissue layer called the dermis. The dermis lies on the subcutaneous tissues that are composed predominantly of adipose tissue. The skin is the largest organ of the body with an average surface area of between 1.5 and 1.8 m^2 and weighs about 16% of the body weight. There are considerable regional variations in the skin – in its thickness which ranges from 0.5–1 mm (eyelids) to 1.5–5 mm (palms, soles), in the presence or absence of hairs, in the amount of pigment, and in the numbers of sweat glands (Figs 2.1–2.4). Histologically, skin is described as thick or thin; a distinction largely based on the epidermal thickness.

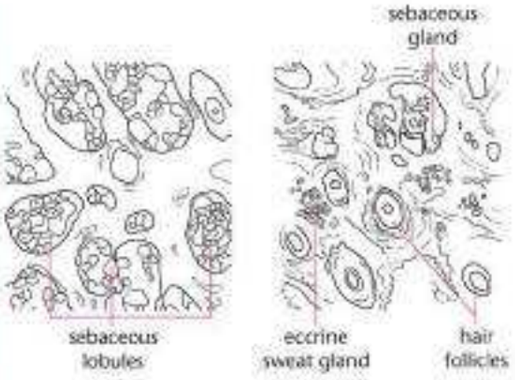




Figs 2.1 and 2.2 Marked regional variations of normal skin structures. Sections from the fingertip of a young male (left; note the conspicuous epidermal ridges), and the abdomen of a young female (right; note the thick dermis and relative paucity of appendage structures).







Figs 2.3 and 2.4 Marked regional variations of normal skin structures. Sections from the nose of young female (left; note the conspicuous sebaceous glands) and the scalp of elderly female (right; note the location of the hair follicles within the subcutaneous fat).

The lower surface of the epidermis is undulating with indentations (the rete ridges or epidermal ridges) intervening between the dermal papillae. The rete ridges increase the surface area of the avascular epidermis that is exposed to the dermal blood vessels (from where the epidermal cells receive oxygen and nutrients). The epidermis has a high metabolic rate, particularly in comparison to the dermis, and employs anaerobic glycolysis as its main form of cellular metabolism. Human epidermal stem cells are concentrated on the rete ridges.

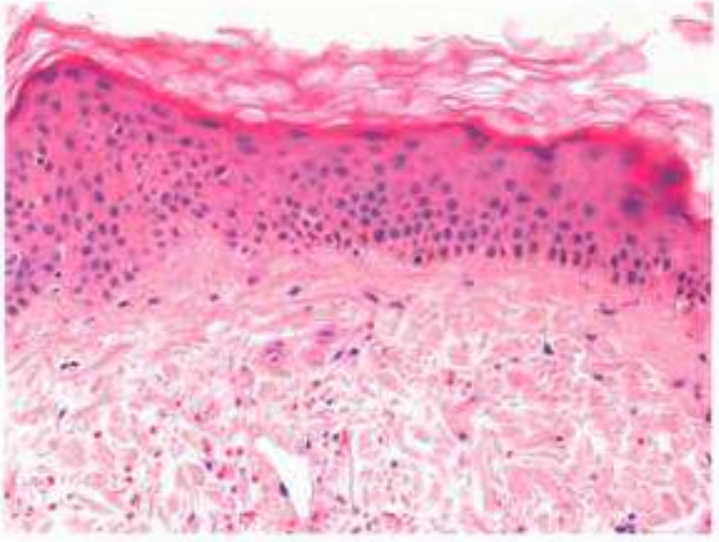
In some hairless parts of the body (fingers, palms, toes and soles) the epidermal surface is covered by raised ridges of skin known as friction or papillary ridges (prints of the friction ridges on the fingers are 'fingerprints'). The friction ridges assist in gripping rough and smooth wet surfaces, and amplify vibrations triggered when fingertips brush across an uneven surface, better transmitting the signals to sensory nerves involved in fine texture perception. The sweat pores, where the sweat glands located in the dermis discharge sweat at the skin surface, are found at the top of the friction ridges.

Structure of the epidermis

The epidermis is a stratified squamous epithelium composed of keratinocytes, melanocytes, Langerhans' cells and Merkel cells. Between 85–95% of the cells in the epidermis are keratinocytes that are embryologically of ectodermal derivation. The keratinocytes are arranged in four or five layers that can be recognized at a light microscopic level (Fig. 2.5).

- Basal cell layer (stratum basale or stratum germinativum)
- Prickle cell layer (stratum spinosum)
- Granular layer (stratum granulosum)
- Clear cell layer (stratum lucidum) (only seen in thick skin)
- Keratin, corneal or horny layer (stratum corneum)

The basal cells form a single layer of cells resting on the basement membrane. In tissue sections, they are smaller (7–15 μm) than the other keratinocytes (prickle cells are 10–15 μm, granular cells are 20–25 μm and corneal cells are 10–30 μm) and have a darker staining nucleus. They produce hemidesmosomes and the basal lamina that attach the epidermis to the underlying dermis (Fig. 2.6). The hemidesmosomes are complex structures containing desmoplakin and cadherin proteins that anchor cytoplasmic keratin filaments into the basal lamina using integrin cell adhesion proteins. The basement membrane can be seen with light microscopy as a stained structure anchoring an epithelial layer (Fig. 2.7). This encompasses the basal lamina secreted by epithelial cells and typically a reticular lamina secreted by other cells, but these can only be distinguished under the higher magnification of an electron microscope. The basal cells are the epidermal stem cells. While some basal cells are



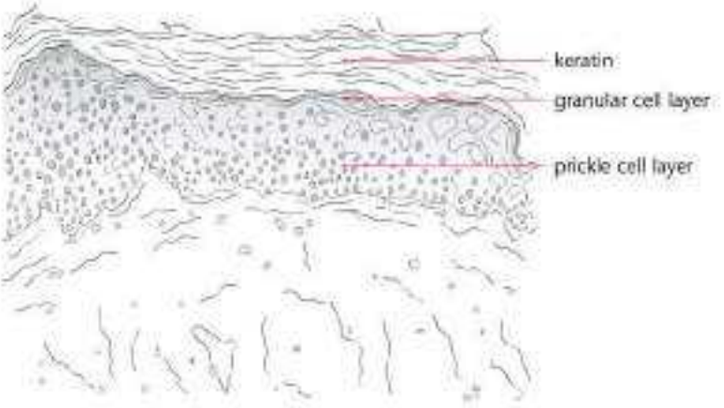
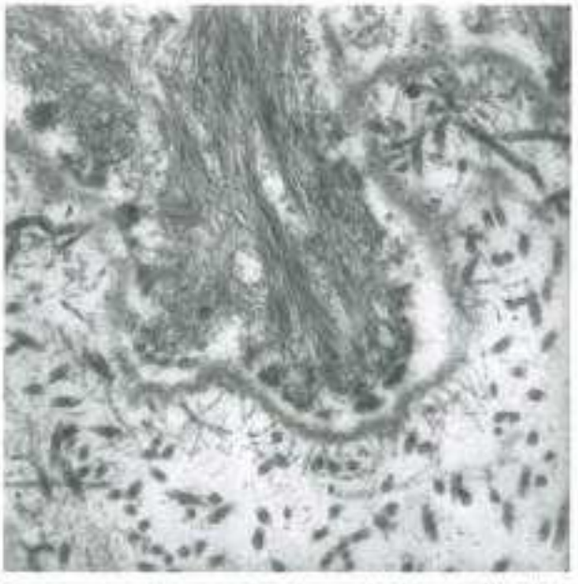


Fig. 2.5 Normal skin. Orthokeratosis overlies an epidermis that is 7–8 cells thick. The upper dermis is mostly eosinophilic staining collagen with scattered fibroblasts and some dermal vessels. (H&E stain).



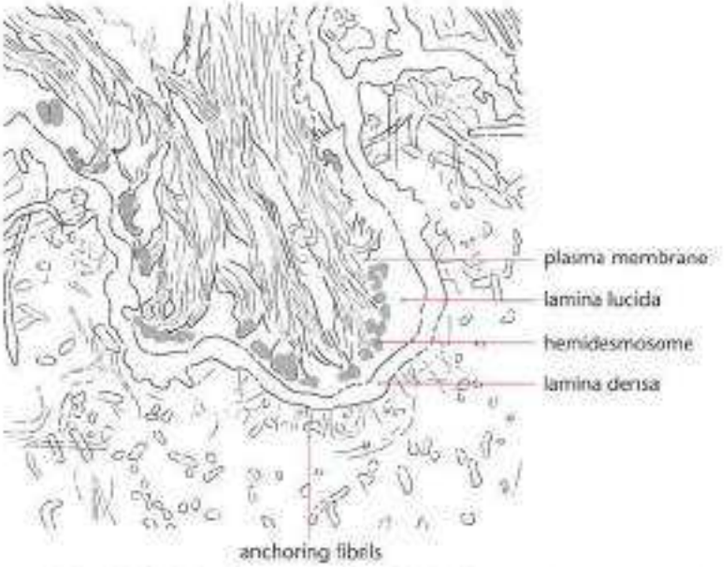


Fig. 2.6 Basement membrane region of normal epidermis. Note the hemidesmosomes, lamina lucida, lamina densa and anchoring fibrils (Electron photomicrograph).

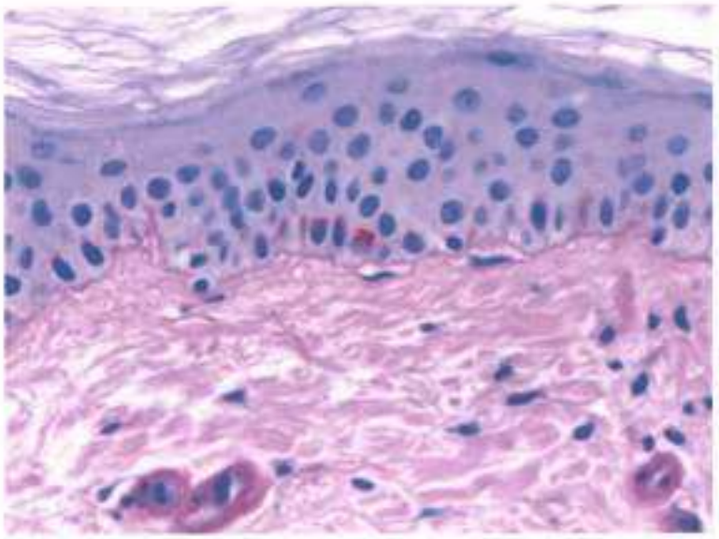


Fig. 2.7 Basement membrane of normal epidermis. The basement membrane is stained pink with Periodic acid-Schiff stain.

dividing, others are moving out of the basal layer into the prickle cell layer. The basal layer is self-renewing – in order to maintain a stable stem cell population, 50% of the daughters of stem cells in each cell generation must remain as stem cells whilst the other 50% leave the basal layer. The EGF, FGF, Wnt, Hedgehog, Notch, BMP/TGFβ, and integrin signalling pathways are all involved in controlling this process of epidermal renewal. Mutations in components of these pathways can lead to the development of some epidermal cancers.

The next layer is the prickle cell layer – so called because the desmosomes between neighbouring keratinocytes produce 'prickles' or 'spines' that are so evident if there has been some shrinkage in the tissue processing prior to section cutting (Fig. 2.8). There are several hundred desmosomes on each keratinocyte. The desmosomes are composed of two plaques on adjacent cells (containing desmoplakin and other proteins) connected by cadherin molecules. The prickle cell layer is of variable thickness – from a few to many cell layers – depending on the thickness of the epidermis. Much of the cytoplasm of the prickle cells is filled with 10 nm diameter intermediate filaments of the keratin family. These keratin filaments are arranged in fibrils or bundles known as tonofilaments (Fig. 2.9). The tonofilaments loop

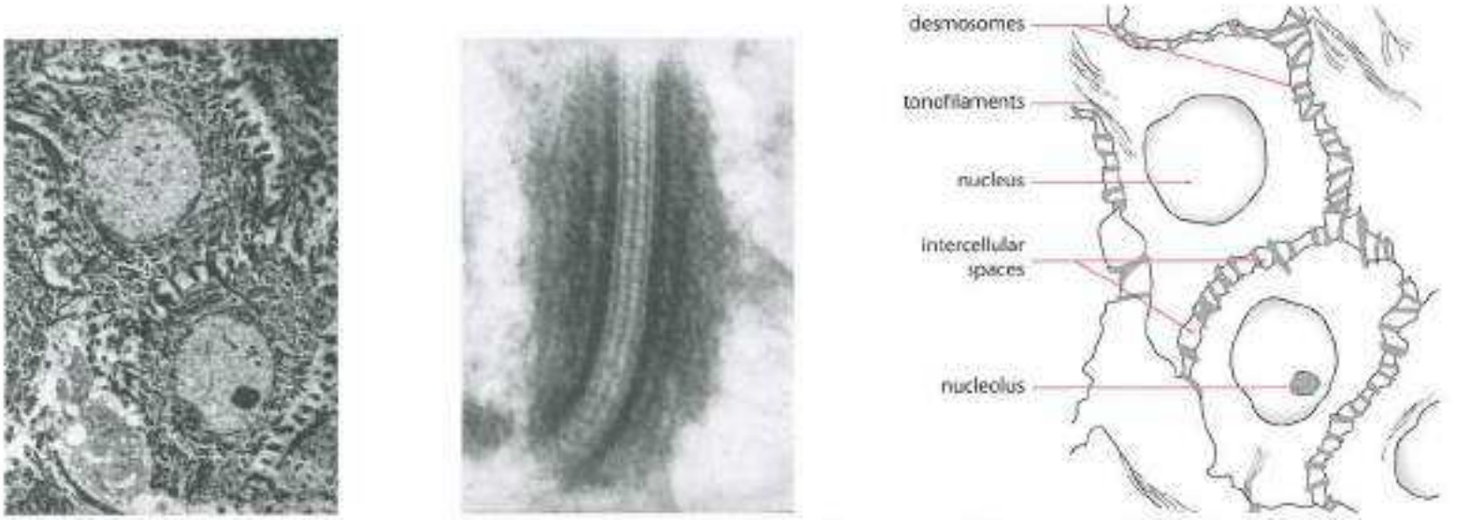


Fig. 2.8 Prickle cell layer. The conspicuous desmosomes can be seen on the left and the multilayered nature of the desmosome (intercellular bridge) is clearly seen on the right. (Electron photomicrographs: left, ×2200 and right ×71 000.)

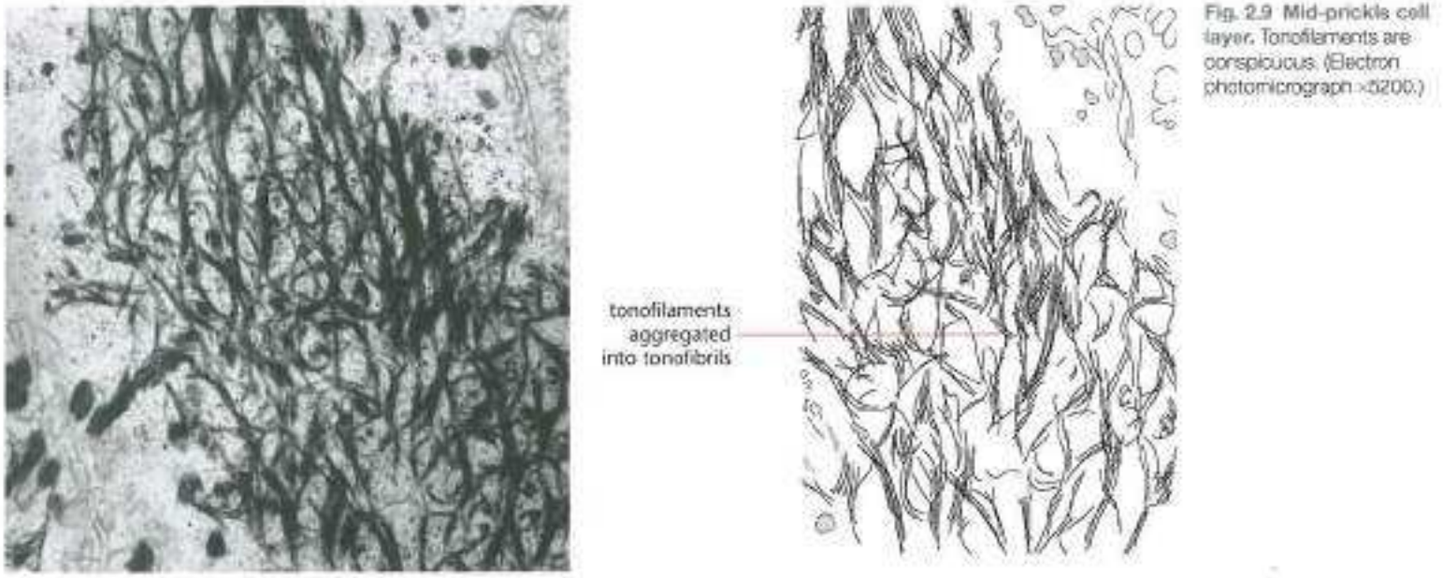
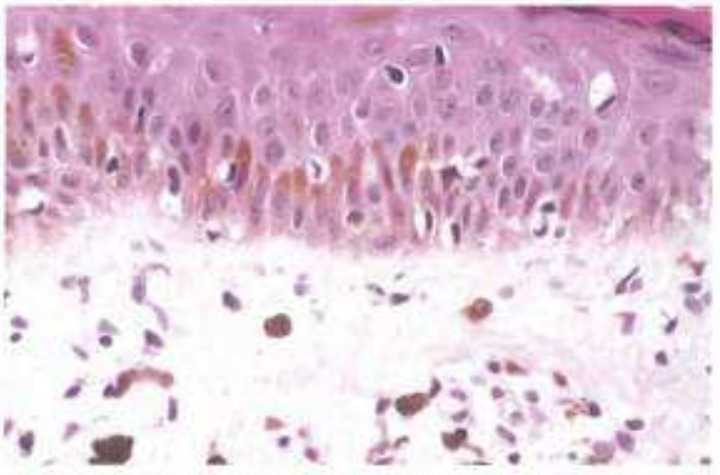


Fig. 2.9 Mid-prickle cell layer. Tonofilaments are conspicuous. (Electron photomicrograph ×5200.)

Fig. 2.10 The granular cell layer. Keratohyalin and membrane-coating granules are present; the lamellated structure of membrane-coating granules is shown in the inset. (Electron micrograph ×17 500; inset ×48 000.)



Figs 2.11 Melanocytes. These appear as clear cells in the basal layer of the epidermis. Pigment is abundant in this section from a black African (H&E stain).

Fig. 2.12 Melanocytes and Langerhans' cells. Melanocytes (basal cell layer) and Langerhans' cells (prickle cell layer) in normal skin are stained black/brown. Dendritic processes are conspicuous (immunohistochemical stain for S100 protein).

into the desmosome plaques spreading out into the cytoplasm. The cells also possess small numbers of lamellar granules (or membrane-coating granules) but these become more numerous in the granular cell layer.

The next layer is the granular layer and is two to five cells thick. Here the cells start to lose their nucleus and cytoplasmic organelles, through a degradative mechanism that involves partial activation of the machinery of apoptosis, and keratohyalin granules form within the cytoplasm of the keratinocytes (Fig. 2.10). The keratohyalin granules contain the proteins fillagrin and trichohyalin that aggregate and bundle the tonofilaments. The lamellar or membrane-coating granules secrete their contents in this layer, coating the cell membranes with lipids and so establishing the water barrier in this layer. Transit of cells from the basal layer to the top of the granular cell layer takes an average of 27–28 days.

The next layer is the clear cell layer (so called because it stains poorly) that is only seen in thick skin. It is the first anucleate layer and is 4–6 cells thick.

The final layer is the keratin or corneal layer that is of very variable thickness (5–10 cells thick over the eyelids, dozens of cells thick over the palms and soles). The cells are polygonal, flattened, anucleate squamous cells ('squames') that are filled with keratin filaments and eventually desquamated from the skin surface (about 1.5 g per day). The average epidermal transit time (from basal layer to desquamation) is 52–75 days so the outer layers of the epidermis are replaced a thousand times over in the course of an average human lifetime.

Melanocytes

Melanocytes are present in the normal epidermis, in the uvea of the eye (the iris and choroid), the meninges, the inner ear, the oesophagus and the anus. Embryologically, they are derived from the lateral margins of the neural tube in humans (the 'neural crest' of lower animals) followed by migration through mesenchyme with subsequent invasion of epidermis. The migrating cells are believed to be oligopotent precursors – this may explain the 'neuronization' of naevus cells that is seen in some intradermal naevi. Histologically, melanocytes are seen as clear cells in the basal layer on H&E staining (Fig. 2.11) (in contrast to Langerhans' cells that are the clear cells seen mainly in the prickle cell layer). Melanocytes comprise 5–10% of the cells in the basal layer of epidermis so there are typically between 1000 and 2000 melanocytes per square mm of skin. Although their size can vary, the cell body of a melanocyte is approximately 7 μm in diameter. Cytoplasmic extensions of a single melanocyte establish contact with an average of 36 keratinocytes in the basal and prickle cell layers (the so-called 'epidermal unit') (Fig. 2.12).

All ethnic groups possess a similar concentration of melanocytes in their skin; the melanocytes in some individuals and ethnic groups more or less frequently express the melanin-producing genes, thereby altering the concentration of skin melanin. Melanocytes synthesize the pigment melanin from the amino acid tyrosine via a complex biosynthetic pathway that is catalysed by the enzyme tyrosinase. There are several different forms of melanin – that in skin is eumelanin (black – the most abundant

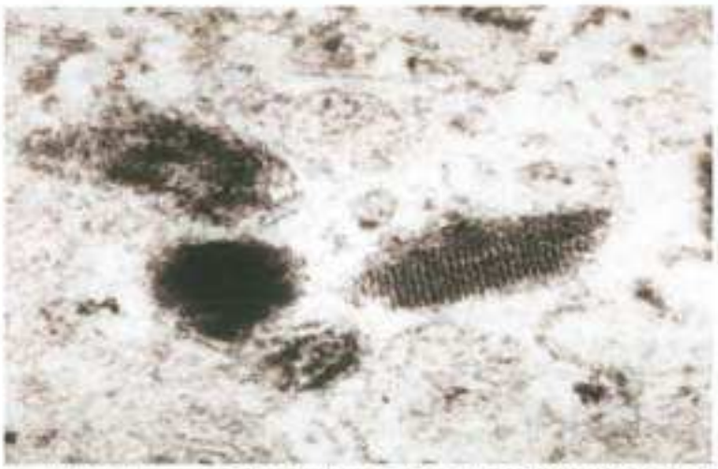


Fig. 2.13 Melanosomes. These are from a patient with malignant melanoma and their lamellated internal structures can be clearly seen. (Electron photomicrograph ×200 000).

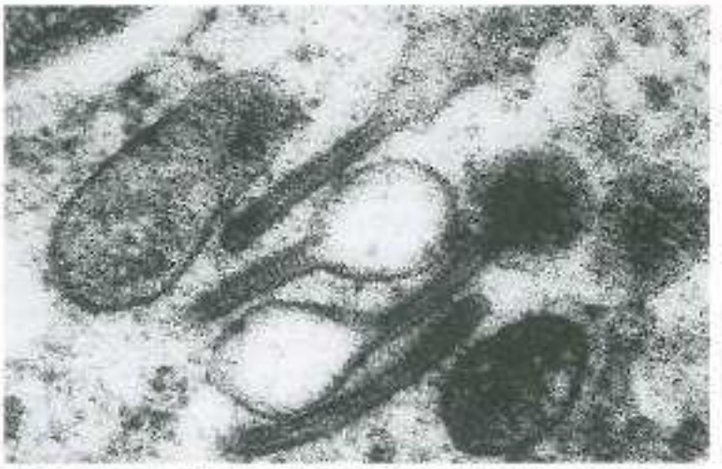


Fig. 2.14 Langerhans' cells. The 'handles' of the characteristic racquet-shaped inclusions of Langerhans' cells have a trilaminar structure with cross-striations. (Electron photomicrograph, ×112 000.)

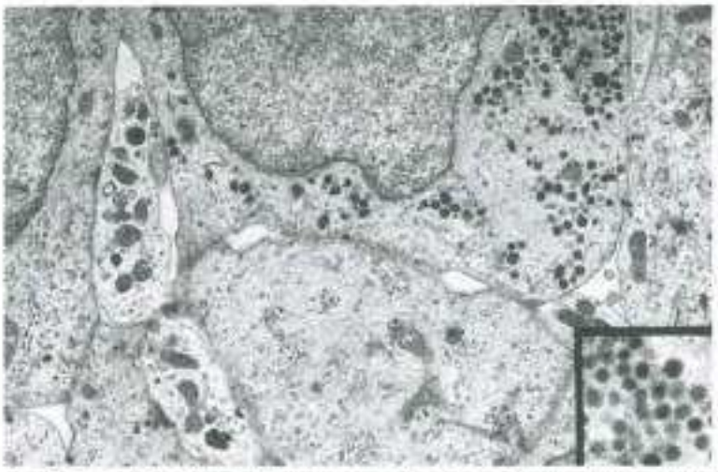


Fig. 2.15 Merkel cell typified by intracytoplasmic membrane-bound granules (inset). Electron photomicrograph, ×16 000, (inset) ×40 000. By courtesy of Prof A.S. Breathnach, Electron Microscopy of Cutaneous Nerves and Receptors. *The Journal of Investigative Dermatology*, **69:** 8–26, 1977; Williams & Wilkins Co.

pigment) and pheomelanin (red). Melanin synthesis takes place in specialized subcellular organelles called melanosomes (Fig. 2.13). Once the melanin granules are formed, they are rapidly transferred via the melanocyte's cytoplasmic extensions to neighbouring keratinocytes and so, in tissue sections of normal skin, the melanocytes appear clear and the keratinocytes appear pigmented.

Langerhans' Cells

Langerhans' cells are present in the normal epidermis and are also normally located in the dermis, mucosa and lymphoid tissues (where they are also known as 'veiled' cells). Langerhans' cells are one of the dendritic cells of the immune system and are highly specialized antigen-presenting cells. They present antigens to T cells to initiate adaptive immune responses. Langerhans' cells are named after Paul Langerhans (1847–1888) who was Professor of Pathological Anatomy at Freiburg in Germany.

Histologically, Langerhans' cells are found most abundantly in the prickle cell layer where they can be seen as cells with clear cytoplasm and elongated, kidney bean-shaped nuclei. They account for 4% of epidermal cells but, because of their dendritic morphology, they account for 25% of the cell surface area. On average, the cytoplasmic extensions of one Langerhans' cell are in contact with 53 keratinocytes. Immunohistochemically, Langerhans' cells are positive for S100 protein (a family of calcium-binding regulatory proteins that couple extracellular stimuli to cellular responses) (Fig. 2.12), CD1a (a transmembrane glycoprotein that mediates the presentation of primarily lipid and glycolipid antigens of self or microbial origin to T cells) and fascin (a 55 kD actin cross-linking protein that is involved in the formation of dendritic processes). They also contain langerin (CD207), a type II transmembrane C-type lectin that initiates the formation of Birkbeck granules (Fig. 2.14), characteristic structures found in the cytoplasm of Langerhans' cells by electron microscopy.

Merkel Cells

Merkel cells are oval receptor cells found in the skin that have synaptic contacts with somatosensory afferents. They are involved in the sense of light touch discrimination of shapes and textures. Experiments with genetic knockout mice have shown that Merkel cells are essential for the specialized coding by which afferent nerves resolve fine spatial details. Merkel cells are derived from epidermal progenitors in mammalian embryonic development. They are located in the basal layer of the epidermis (especially in the rete ridges of lips and fingertips), in follicular epithelium and in some mucosa. Merkel cells are named after Friedrich Sigmund Merkel (1845–1919) who was a leading German anatomist and histopathologist. 80% of Merkel cell carcinomas contain Merkel cell polyomavirus – a 'new' virus discovered in 2008 – associated with the tumour cell DNA. The ultrastructural appearance of Merkel cells is characteristic with 80–100 nm diameter, membrane-bound, dense-core granules that contain a variety of neuropeptides (Fig 2.15).

Epidermal appendages

Hair

Skin may be hairy or hairless. Hairless skin covers the palmar and plantar surfaces and the ventral aspects of the fingers and toes, the lips, and around the urogenital orifices (the inner aspect of the prepuce and glans penis and the inner parts of the female genitalia).

Hairy skin shows great variation in the number and thickness of hairs – consider the eyelid, eyebrow, scalp, beard area in men, and the forearm. Hair is made up almost entirely of keratin and is produced by the hair follicles. Hair follicles are formed from a hair bulb composed of epithelial hair matrix cells arranged around a vascularized connective tissue papilla. Cell division in the hair matrix epithelium produces the hair fibre and inner root sheath (on average, scalp hair grows just over 1 cm a month). The diameter of human hair varies from 17 to 180 μm.

The hair follicle develops as an oblique or curved downgrowth of epidermal cells into the dermis or subcutaneous fat, becoming canalized to form the relatively immobile external root sheath of the hair. Proliferation of germinative cells at the base of the hair forms the inner root sheath and the hair shaft, which lie within the follicular canal. In the region of the hair bulb, the external root sheath is continuous with the germinative cells of the hair matrix. Distally, the enlarged hair bulb encloses the connective tissue hair papilla that is continuous with the periadnexal fibrous tissue sheath. The hair papilla is richly vascularized and contains abundant nerve endings, both myelinated and non-myelinated.

By about the fifth to sixth month of intrauterine life, the fetus is covered by a fine layer of very delicate lanugo hairs. This is lost before birth except on the scalp, the eyebrows and the eyelashes, where the hair becomes coarser and stronger. Shortly after birth, a new growth of downy vellus hair covers the body of the infant. At around puberty, coarse pigmented hairs develop in the pubic and axillary regions and on the face and chest of males; these are called terminal hairs. There are four main types of hair: straight, wavy, helical and spiral.

The fully developed hair has the following structure (Figs 2.16 and 2.17). Enclosing the hair follicle is the vascular periadnexal fibrous tissue sheath, which is separated from the cells of the external root sheath by a basement membrane. The external root sheath superficially consists of all layers of the epidermis, whereas distal to the entrance of the sebaceous duct it consists only of the prickle cell layer. In this region, the cells are markedly vacuolated owing to the presence of glycogen. The germinative hair matrix cells, which give rise to all layers of the internal root sheath and hair shaft, have dark basophilic cytoplasm, large vesicular nuclei and contain melanocytes. The internal root sheath consists of three concentric layers: Henle's layer, which is one cell thick, Huxley's layer, which is two cells thick, and the cuticle, which consists of a layer of flattened scales. All of these cells undergo keratinization.

The shaft of the hair consists of a cuticle, a cortex and a medulla (the last is absent from lanugo and vellus hairs). The cuticle consists of a single layer of flattened scales. The cortical cells undergo atypical keratinization in that keratohyaline granules are absent and the cells undergo a gradual transformation from living epidermal cells into keratin. The medulla, if present, consists of layers of polyhedral cells. The cuticle of the internal root sheath interlocks with the cuticle of the shaft so that they function as one structure during growth up the follicular canal.

The arrector pili muscle arises within the papillary dermis and passes obliquely downwards to its insertion into the perifollicular connective tissue sheath. Contraction of the arrector pili makes the hair 'stand on end' and brings on 'goose-pimples' or 'goose bumps'.

Hair undergoes cyclical periods of growth, divided into three phases: anagen, in which there is active hair growth; catagen, associated with involution; and telogen, the resting phase (Fig. 2.18). The cycle is variable in different regions of the body; for instance the duration of eyelashes is about 4 months, whilst that of the scalp is 3–4 years. This is the reason eyebrow hairs are shorter than scalp hairs.

Hair colour is the result of two types of hair pigment. Eumelanin is the dominant pigment in dark-blond, brown, and black hair, while pheomelanin is the dominant pigment in red hair. Blond hair is the result of having little pigmentation in the hair strand. Grey hair occurs when melanin decreases or disappears.

The hair of most mammals is of great importance in temperature conservation. In humans, this function is largely taken over by the subcutaneous fat. Hair has some value as a touch receptor and as a secondary sexual characteristic. The follicular epithelium is of immense value as a reserve of basal cells for epidermal regeneration following trauma.

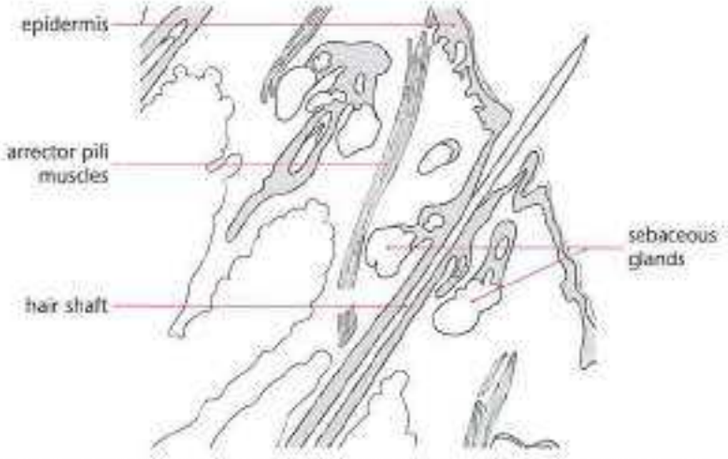


Fig. 2.16 Hair. Section of scalp showing several normal pilosebaceous units with adjacent arrector pili muscles. (H&E stain; courtesy of Dr J. S. Dixon, University of Manchester.)

Sebaceous Glands

A hair follicle and its associated sebaceous gland are referred to as a pilosebaceous unit. The sebaceous glands empty their holocrine secretions (the protein- and lipid-rich sebum) into the hair follicle through the pilosebaceous duct. The sebaceous gland arises as a lateral protrusion of the outer root sheath of the developing hair follicle. It can be first clearly identified at 13–15 weeks of gestation. During fetal life, its secretory product, sebum, is partially responsible for the vernix caseosa, the other constituents being fetal hair and squames. The sebaceous gland is largely inactive during prepubertal life but enlarges and becomes functionally active during and after puberty. While fairly widespread in distribution, sebaceous glands are not found on the palms or soles but are concentrated about the face and scalp, in the midline of the back and in the perineum. As can be imagined from their development, they almost invariably drain into the follicular infundibulum. Exceptions do occur, however, including the Meibomian glands at the rim of the eyelids and Montgomery's tubercles of the areola of the breast.

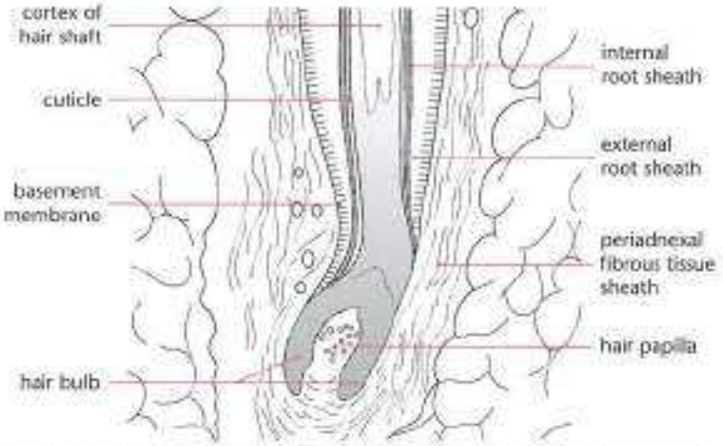


Fig. 2.17 Hair. Longitudinal section showing the various layers found in a normal hair (Haematoxylin and eosin stain; courtesy of Dr J. S. Dixon, University of Manchester).

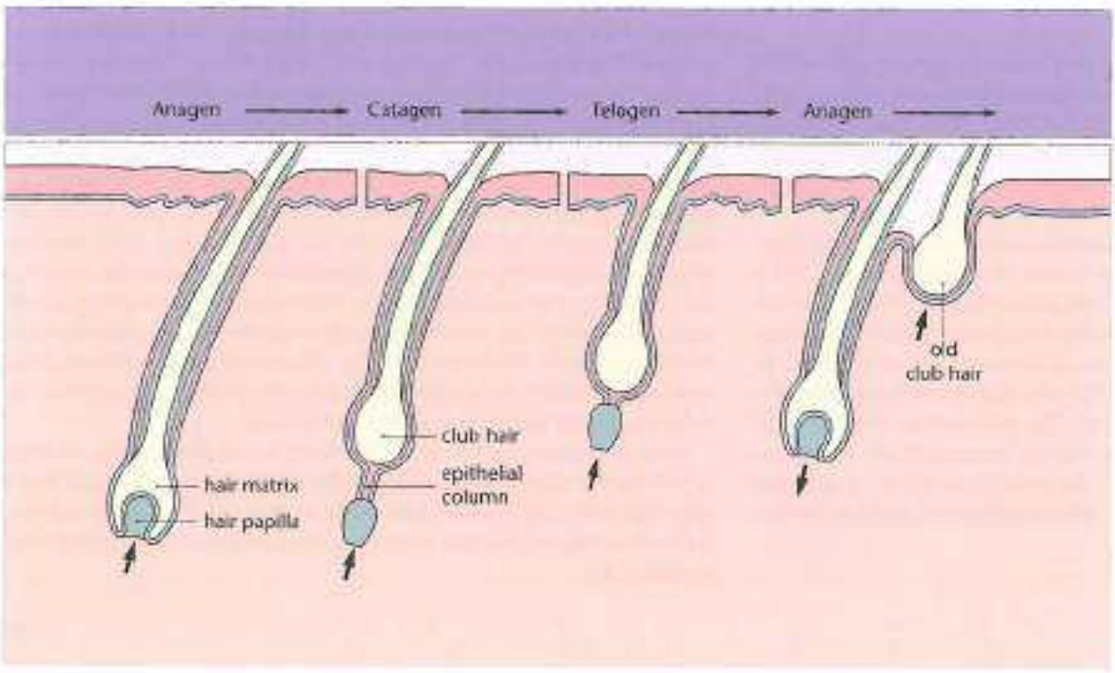


Fig. 2.18 Growth cycle of hair. During catagen, the matrix of the hair is enclosed within a shortened retracted external root sheath as it grows up the follicular canal, forming a club hair. A residual epithelial column (probably derived from both hair matrix and external root sheath) connects the club hair and the hair papilla. During telogen, the club hair progresses further towards the surface and the epithelial column contracts to form a nest of cells around the base of the club hair. The hair papilla also ascends to lie close to the epithelial nest. With the onset of anagen, a new hair matrix forms and, with the subjacent hair papilla, descends to its previous resting level. A new hair then develops that eventually dislodges the old club hair.

Fig. 2.19 Sebaceous gland. Section from the nose showing numerous sebaceous lobules arising from a hair follicle (H&E stain).

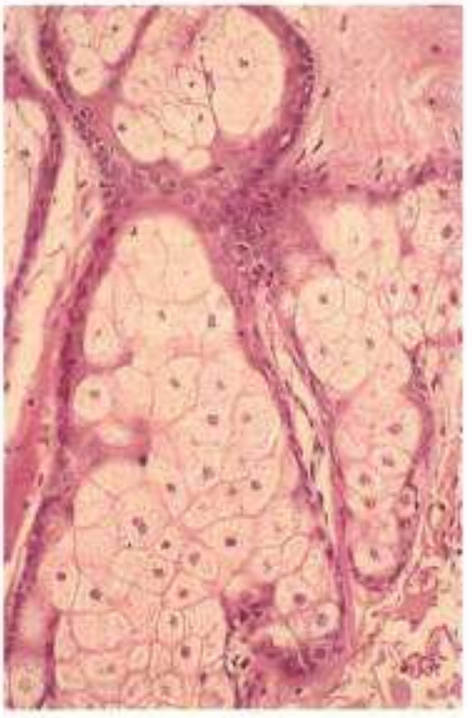


Fig. 2.20 Sebaceous gland. Higher magnification view of sebaceous gland showing outer layer of basophilic germinative cells and inner lipid-laden mature cells (H&E stain).

Histologically, the sebaceous gland consists of several lobules lying adjacent and connected to a hair follicle (Fig. 2.19); each lobule consists of an outer layer of cuboidal basophilic cells from which arises the inner zone of lipid-laden vacuolated cells (Fig. 2.20). Its secretions drain into the sebaceous duct. Secretion appears to have a circadian rhythm, largely under the control of androgens and appearing to be inhibited by oestrogens. Therefore, male sebaceous glands are larger and more functionally active than those of females.

Sebum is a lipid mixture of triglycerides, wax monoesters, free fatty acids and squalene. Its function in humans, although uncertain, possibly includes waterproofing, control of epidermal water loss and a protective function inhibiting the growth of fungi and bacteria.

Apocrine Glands

Apocrine glands are found predominantly in the anogenital and axillary regions. They are derived from the epidermis and develop as an outgrowth of the superior portion of the follicular epithelium. Their exact function is unclear but they are thought to represent scent glands. Similar to sebaceous glands, apocrine glands are rather small in childhood, becoming larger and functionally active at puberty.

Apocrine glands consist of two distinct components: a secretory component situated in the lower reticular dermis or subcutaneous fat and a tubular duct linking the gland with the pilosebaceous follicle at a site above the sebaceous duct. Microscopically, the secretory portion comprises an outer layer of myoepithelial cells and an inner layer of cuboidal to columnar eosinophilic cells (Fig. 2.21). The duct portion consists of a double layer of cuboidal epithelium. The mechanism of control of apocrine glands is uncertain but they respond to sympathetic adrenergic stimuli initiated by emotional stress. The unpleasant odour of apocrine secretion, which is initially odourless, is from breakdown products formed by the cutaneous bacterial flora.

Eccrine Sweat Glands

Eccrine sweat glands derive from a specialized downgrowth of the epidermis (the 'eccrine germ') at about the fourth month of intrauterine life. They are found everywhere on the skin but are not present in the nail beds or the mucous membranes. Their sites of maximum distribution are the palms, soles, axillae and forehead. Histologically, they are divided into four subunits: a coiled secretory gland, a coiled dermal duct, a straight dermal duct and a coiled intraepidermal duct. The secretory component lies in the lower reaches of the reticular dermis or around the interface between the dermis and subcutaneous fat. It consists of an outer layer of contractile myoepithelial cells and an inner layer of secretory cells (Fig. 2.22). The latter consists of two cell types: large clear cells, responsible for its watery secretions, and smaller darkly staining mucopolysaccharide-containing cells. Between adjacent clear cells are canaliculi, which open into the lumen of the tubule. The dermal duct is formed from a double layer of cuboidal basophilic cells. The duct is not just a conduit but has a biologically active function in modifying the composition of eccrine secretion, in particular the reabsorption of water. The intraepidermal duct opens directly onto the surface of the skin.

Function of the eccrine gland is under the control of cholinergic postganglionic sympathetic nerve fibres. The activity of the secretory component is stimulated by thermal, mental and gustatory functions. Thermal sweating is dependent on an intact hypothalamus (activated by temperature changes of its perfusing blood). Thermoregulatory sweating occurs especially on the face and upper trunk. Mental sweating is presumably under the control of the limbic lobe. This particularly induces palmar sweating. Gustatory sweating of the lips, forehead and nose (as after a hot spicy meal) is of uncertain function and control.

Sweat of eccrine type has a basic similarity to the plasma from which it is derived; the duct is responsible for the modifications that occur. It is a clear hypotonic solution with a pH in the range 4–6.8. In addition to water, it contains sodium, chloride, potassium, urea, lactate, ammonia and some amino acids.

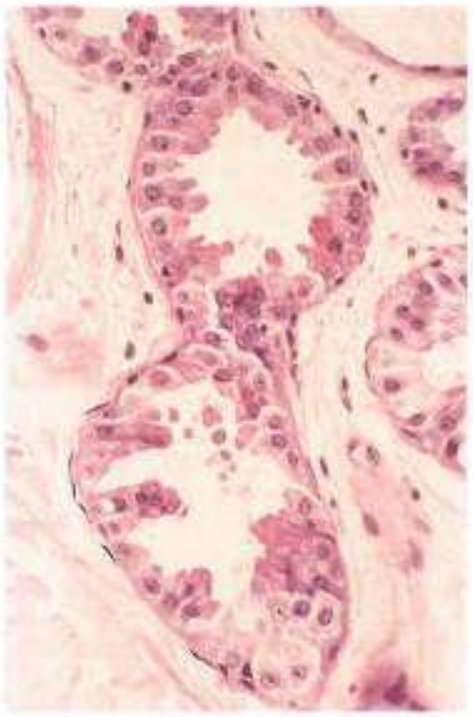


Fig. 2.21 Apocrine gland. Section from the axilla showing apocrine glands; note the decapitation secretion.

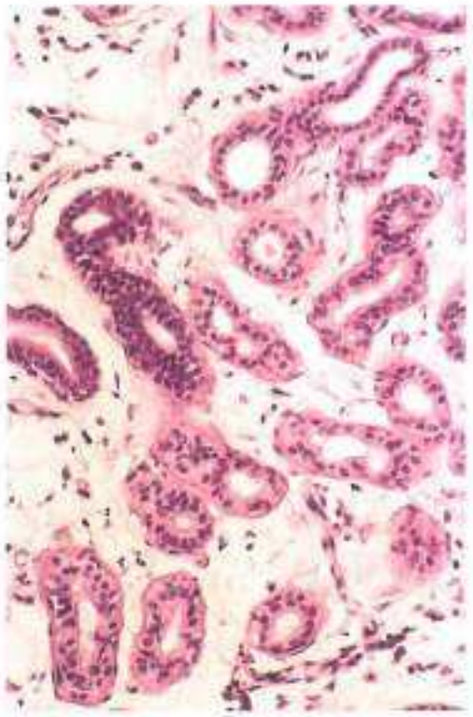


Fig. 2.22 Eccrine gland. Cross-section of normal eccrine gland with darker-staining ductal system (H&E stain).

The nail

Like hair, the nail is formed by an invagination of epidermis into dermis. The formed keratin is tough and densely adherent, rendering the nail plate a remarkably resilient structure.

Anatomically, the nail consists of three distinct parts: the root, the nail plate and the free edge (Fig. 2.23). The root is overlapped by the proximal nailfold, which is continuous at its margins with the lateral nailfolds. Overlying the proximal portion of the nail plate is a thin fold, the eponychium, which partially or completely obscures the crescent-shaped lunula, the distal portion of the nail matrix. The lunula is usually completely visible in the thumbnail but is completely covered in the fifth nail. The undersurface of the free margin of the nail is continuous with the hyponychium, the thickened epidermis beneath it. The nail plate lies upon a richly vascularized nailbed, which is continuous proximally with the nail matrix (Fig. 2.24); the epithelia of both undergo keratinization, which, as in hair, occurs in the absence of a granular cell layer. The horny layers of the nailbed and the nail plate are firmly attached, and forward movement of the nail plate is accompanied by forward movement of keratinized cells of the nailbed. On average, nails grow about 0.1 mm per day, growth being faster in summer than in winter and the fingernails growing faster than the toenails.

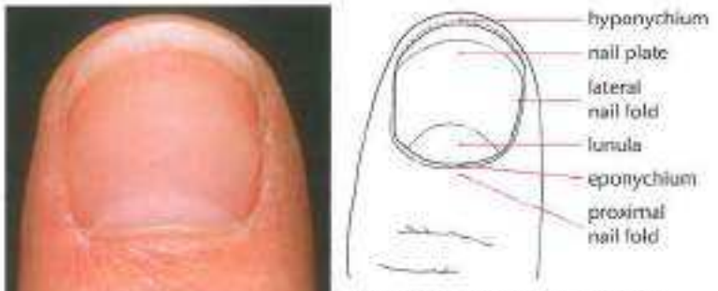


Fig. 2.23 Nail. Macroscopic view of thumbnail showing normal features.

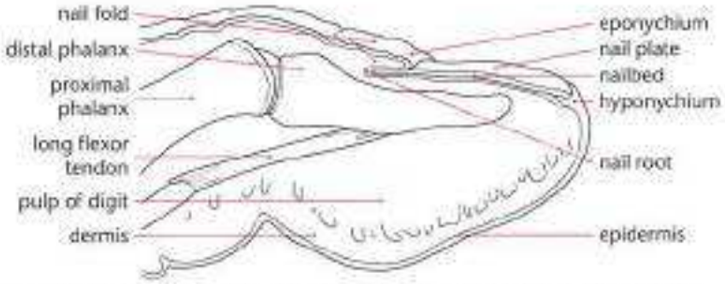


Fig. 2.24 Nail. Sagittal view of thumbnail showing normal features. (Courtesy of Dr P. L. T. Willan, University of Manchester.)

The dermis

Structure of the Dermis

The dermis is formed of two layers – an upper papillary dermis that lies between and immediately beneath the rete ridges of the epidermis and a deeper reticular dermis. The dermis is composed of collagen (70% of dermal proteins), elastic fibres and extrafibrillary matrix. The papillary dermis is formed of fine collagen fibres (mainly collagen type III) whilst the reticular dermis is formed of coarse collagen fibres (mainly collagen type I). The reticular layer also contains fibroblasts, mast cells, nerve endings, lymphatics, and epidermal appendages. Surrounding the components of the dermis is the extra-fibrillary matrix, composed of mucopolysaccharides (primarily hyaluronic acid), chondroitin sulphates, and glycoproteins. The fibroblasts are the main cells in the dermis and are essentially located in the dermal papillae close to the epidermis. They are found only in very low numbers in the reticular dermis. They produce the collagen and elastin fibres. The collagen fibres give the dermis its resistance to strain and traction, while elastin supplies its elastic properties. The reticular dermis accounts for the greater part of the dermis. Here, the elastin and collagen fibres are multidirectional, whereas in the dermal papillae the elastin fibres are mainly oriented perpendicular to the skin surface.

Collagen

Collagen gives the dermis its structural stability. In the papillary dermis, it consists of fine fibres in haphazard arrangement, while in the reticular dermis it consists of broad bundles lying roughly parallel to the epidermal surface (Fig. 2.25). Collagen is formed within the ribosomes of fibroblasts; the essential subunit of collagen is the monomer tropocollagen, which has a molecular weight of approximately 300 000 and is composed of three peptide chains. Each chain has a helical structure and the three chains are intertwined to form a superhelical molecule. The structural stability of collagen is increased by intra- and intermolecular cross-linkages, the latter including side-to-side, end-to-end and overlapping types. This produces an enormously strong fibrillary structure. Collagen characteristically contains the amino acids hydroxyproline and hydroxylysine.

Fig. 2.25 Collagen. High-power view of normal skin showing broad bands of collagen in the reticular dermis (Masson's trichrome stain).

Collagen is not a homogeneous entity but consists of a variety of genetically distinct subtypes: designated types I–X according to morphology, amino acid composition and physical properties. In the dermis, the broad bands of reticular collagen are type I, the most common form, while the finer fibres (also known as reticulin) of the papillary dermis are type III. When longitudinal sections of collagen are examined electron microscopically, they exhibit cross-striations (Fig. 2.26) with a periodicity of approximately 64 nm.

Elastic Tissue

Elastic fibres are intimately associated with collagen. They cannot be identified with haematoxylin and eosin staining but are easily demonstrated by a number of special techniques such as the elastic-van Gieson stain. In the papillary dermis, the elastic fibres are thin and tend to run at right angles to the skin surface, whereas those in the reticular dermis are thicker and tend to lie parallel to the skin surface (Fig. 2.27). Like collagen, elastic fibres are produced by fibroblasts. Ultrastructural examination shows elastic tissue to consist of an amorphous electron-dense component (elastin) in which are embedded microfibrils. Elastic tissue characteristically contains the unusual amino acids desmosine and isodesmosine. While elastic fibres are responsible for cutaneous elasticity, they are also thought (in combination with ground substance) to be responsible for prevention of overextension.

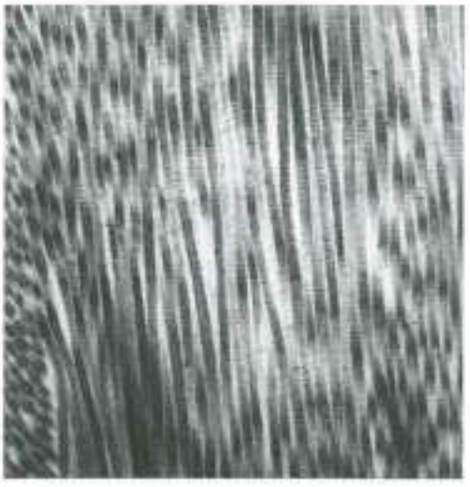


Fig. 2.26 Collagen. Typical cross-striations can be seen. (Electron photomicrograph, ×47 000.)

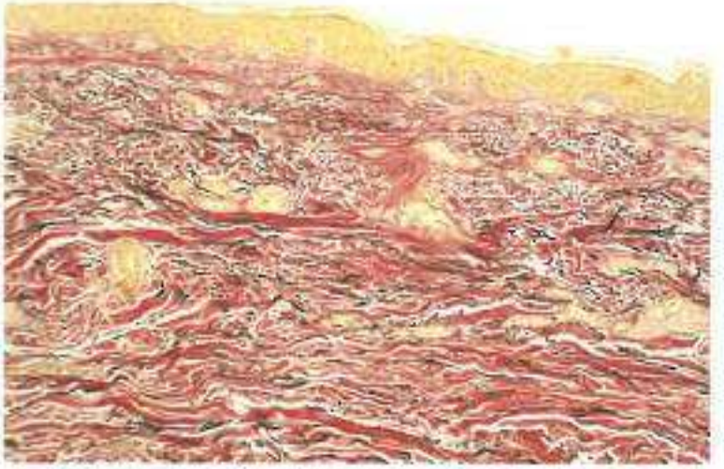


Fig. 2.27 Elastic tissue. Paucity of elastic fibres in the papillary dermis contrasts with their abundance in the reticular dermis (Elastic-van Gieson stain).

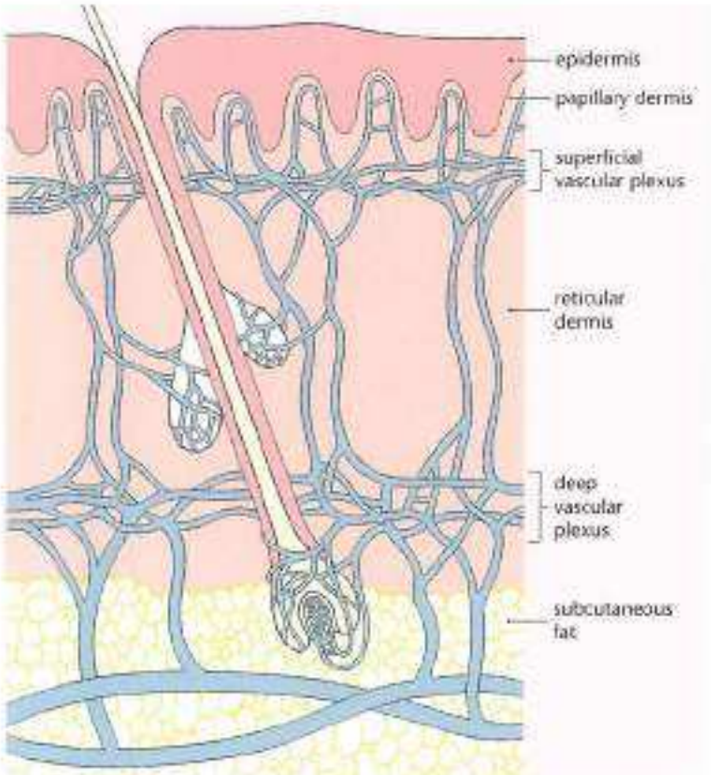


Fig. 2.28 Cutaneous blood vessels. Diagram showing the relationship of the superficial and deep vascular plexuses.

Ground Substance

Ground substance is another product of fibroblasts and accounts for a large proportion of the volume of the dermis but cannot be visualized with routine stains, special stains such as Alcian blue being necessary. Ground substance is not merely an amorphous material in which the fibrous components are embedded but can best be visualized as a gel-like substance existing in intimate chemical relationship with the fibrous components of the dermis. In addition to large quantities of water, it consists of the glycosaminoglycans hyaluronic acid, chondroitin 4-sulphate and dermatan sulphate.

Cutaneous blood vessels

The skin receives an extensive vascular supply from vessels within the subcutaneous fat. From these arise two vascular plexuses linked by intercommunicating vessels (Fig. 2.28); one, the deep vascular plexus, lies in the region of the interface between dermis and subcutaneous fat and the other, the superficial vascular plexus, lies in the superficial aspects of the reticular dermis and supplies the papillary dermis with a candelabra-like capillary loop system. Each loop consists of an ascending arterial limb and a descending venous limb. The collagenous component of the dermis receives only a limited blood supply, most of the capillary systems being associated with the metabolically active epidermis and its appendages.

A specialized cutaneous arteriovenous anastomosis, the Sucquet–Hoyer canal, is found in the dermis of the fingertips and to a lesser extent elsewhere on the body. The canal is surrounded by several layers of modified smooth muscle cells that function as a sphincter. These anastomoses enable the capillary networks of the superficial dermis to be bypassed, thus increasing the venous return from the extremities.

Cutaneous blood flow (under hypothalamic control) is of extreme importance in thermoregulation. Mediated by the sympathetic nervous system, heat loss can be increased or diminished by varying the volume of blood entering the superficial capillary systems. A higher outside temperature results in an increased blood flow to the papillary dermis, accompanied by an increase in eccrine sweat gland secretion. Evaporation of sweat cools the outer parts of the body, with a resultant diminution of temperature of circulating blood. Thus, temperature control depends upon a delicate interplay between vascular and sweat gland function. The dermis also contains an extensive lymphatic system closely associated with the vascular plexuses.

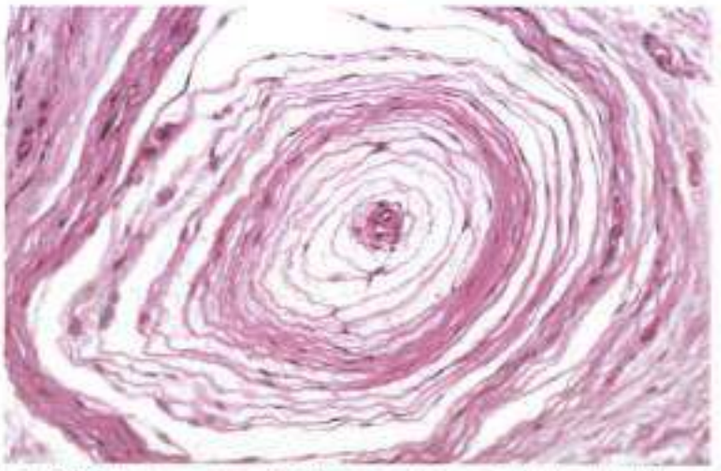


Fig. 2.29 Cutaneous nerves. Pacinian corpuscle showing the lamellated internal structure (H&E stain).

Cutaneous nerves

The skin receives a very large extensive nerve supply. The efferent system responsible for control of the cutaneous vasculature and skin appendages is derived from the sympathetic division of the autonomic nervous system. The afferent system is responsible for the appreciation of cutaneous sensation. Afferent receptors are of three types: free nerve endings, nerve endings in relation to hair, and encapsulated nerve endings. Free nerve endings, of both myelinated and non-myelinated types and of low conduction speed, are mainly responsible for the appreciation of temperature, itch and pain. Hair follicles are supplied by an intricate network of myelinated fibres, some of which ramify as free nerve endings in the perifadnexal fibrous tissue while others enter the epidermis to terminate as expansions in intimate association with Merkel cells in the external root sheath, the so-called tactile discs, which function as touch receptors.

Encapsulated nerve endings are of various types including, in particular, the specialized corpuscles of Meissner and Pacini. Pacinian corpuscles are responsible for the appreciation of deep pressure and vibration and are found in the subcutaneous fat of the palmar aspect of the hand, the plantar aspect of the foot, the dorsal surfaces of the digits and around the genitalia. They are round or oval in shape and are quite large, measuring approximately 1 mm in length. They consist of 20–60 concentric lamellae (modified Schwann cells separated by gelatinous material) lying around an unmyelinated nerve terminal (Fig. 2.29).

Meissner's corpuscles enable the appreciation of touch sensation and are found especially in the dermal papillae of hands and feet and on the front of the forearm. They are oval in shape and measure 30–140 μm in length × 40–60 μm in diameter; they consist of a perineural-derived lamellated capsule surrounding a core of cells and an unmyelinated nerve fibre ending.

Subcutaneous fat

Fat is divided into lobules by fibrous septae and its cells are characterized by large quantities of lipid, which compress the nucleus against the cytoplasmic membrane. Subcutaneous fat is of great importance in thermoinsulation and also functions as a nutritional store.

3 Eczema

The skin has only a limited number of ways in which it can react. As a result, the most common reactive pattern, eczema, is not a homogeneous disorder and does not constitute a diagnosis in itself. It is a set of symptoms and physical signs, which rather like anaemia, require classification to determine its origins. The subtypes are known as:

- Atopic eczema
- Seborrhoeic eczema (infantile and adult)
- Discoid (nummular) eczema
- Pompholyx (hand and foot) eczema
- Juvenile plantar dermatosis
- Lichen simplex
- Lichen striatus
- Varicose eczema (Ch. 23)
- Contact dermatitis (Ch. 4)

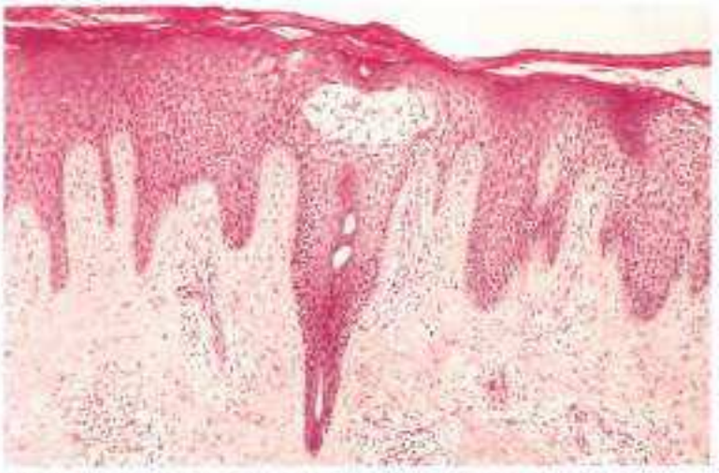


Fig. 3.1 Acute eczema. There is hyperkeratosis, acanthosis and marked intercellular oedema (spongiosis) with resultant microvesiculation.

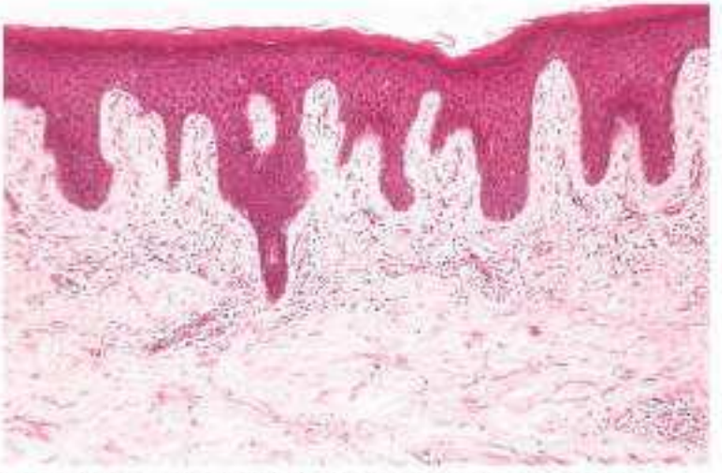


Fig. 3.2 Chronic eczema. There is hyperkeratosis, marked acanthosis and prolongation of the epidermal ridges. Spongiosis is minimal here. Within the dermis there is a lymphocytic infiltrate around dilated blood vessels.

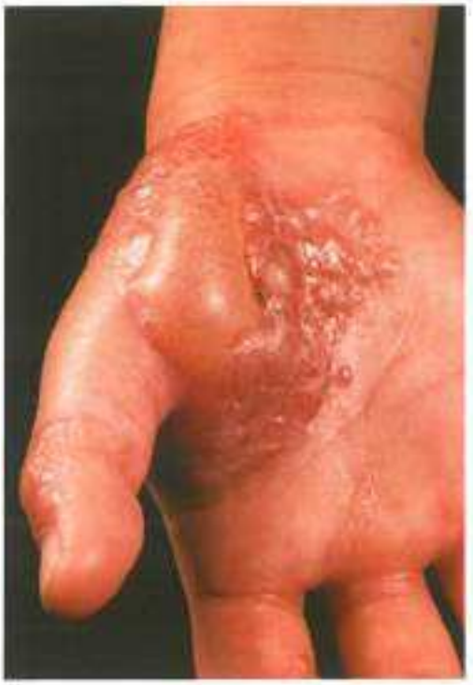


Fig. 3.3 Acute eczema. Vesicles, which may become confluent and bullous, dominate the clinical picture, as in this patient with an acute pompholyx.

The terms 'eczema' and its relative 'dermatitis' are unsatisfactory. Some use them synonymously; some prefer atopic dermatitis to atopic eczema because true eczematous changes are not present, while others prefer to reserve dermatitis for a disorder with an exogenous cause (e.g. contact dermatitis) and eczema for an endogenous disease. However, this is also unsatisfactory because what is now called endogenous may in due course be shown to have an exogenous explanation. Moreover, the term dermatitis is also used as a prefix for quite separate and unrelated diseases, such as dermatitis herpetiformis, perioral dermatitis and dermatitis artefacta, which only confuses matters further.

Eczema has various stages, which depend on the degree of inflammation in the skin. These are known as acute, subacute or chronic, and one or all of these stages may be present in a patient at any one time. They can be more easily understood by considering the pathology (Figs 3.1 and 3.2). The blood vessels are dilated (seen clinically as erythema) and are surrounded by inflammatory cells, which migrate into the epidermis, resulting in a varying amount of oedema both between the epidermal cells (spongiosis) and within them. These cells consequently malfunction and so the epithelium is thickened (acanthosis) with excess production of keratin (hyperkeratosis) and scaling.

Clinically, the oedema produces red papules, which may become bullae (Fig. 3.3), with a serous exudation (acute or wet eczema) if the oedema

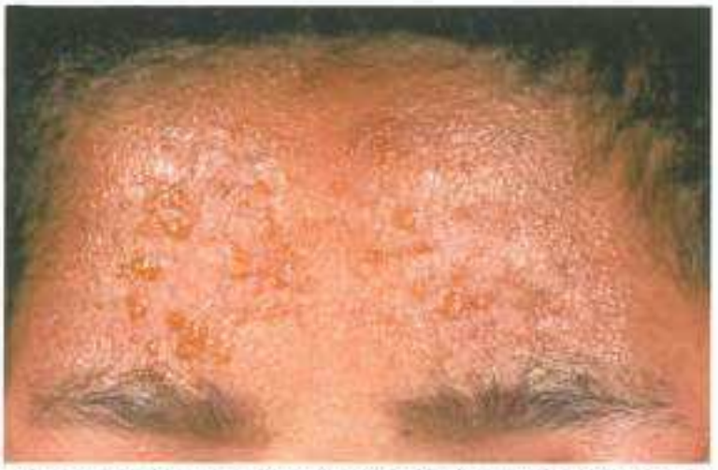


Fig. 3.4 Acute eczema. There are papules and vesicles with oozing of serum in this patient with atopic dermatitis. This could also represent contact dermatitis, but patch tests were negative.

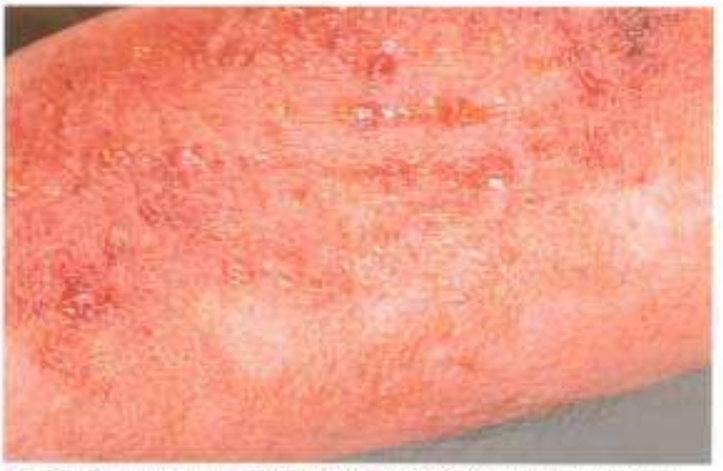


Fig. 3.5 Acute eczema. There are papules and vesicles on a background of erythema in this patient who had a primary irritant dermatitis.

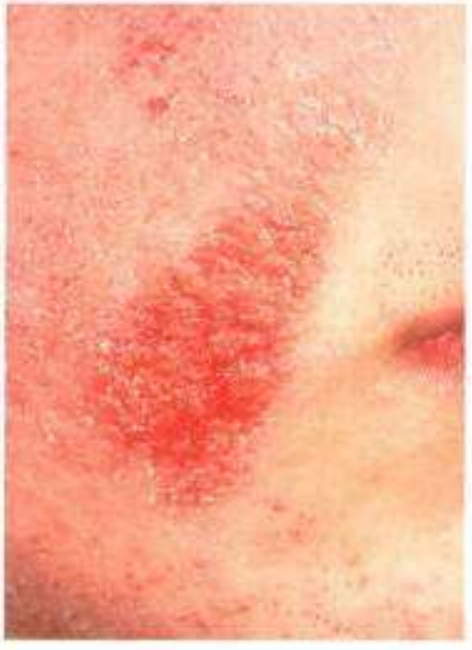


Fig. 3.6 Subacute eczema. There is glistening of serum, redness, scaling and crusting. Secondary infection frequently supervenes.

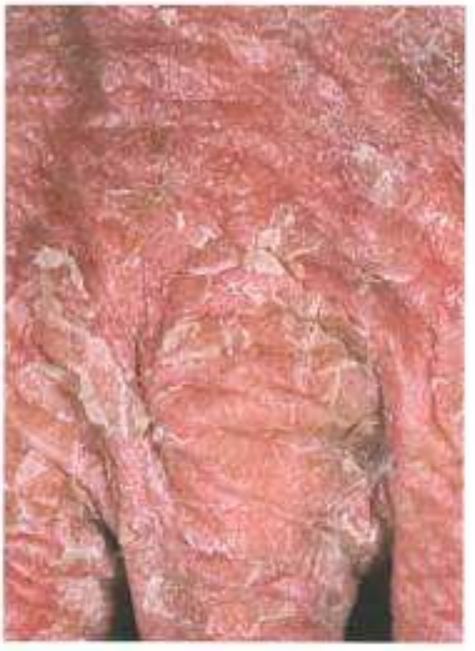


Fig. 3.7 Chronic eczema. The skin is dry, pink and scaly with a tendency to splitting (fissuring) of the skin as in this patient with a photosensitive eruption (chronic actinic dermatitis) on the backs of the hands.

is considerable or papulovesicles (Figs 3.4 and 3.5). In less acute cases (subacute eczema), there is a glistening of serum and crusting (Fig. 3.6). In chronic or dry eczema, the acanthosis and hyperkeratosis predominate and the skin is red, dry, scaly, slightly thickened and with a tendency to crack and fissure (Fig. 3.7). The papules, particularly in pigmented races, are often centred around hair follicles and the appearance is known as *follicular eczema* (Fig. 3.8) or *disseminate and recurrent infundibulofolliculitis*.

Eczema is intensely pruritic in all forms except seborrhoeic eczema. As a result, patients scratch and rub the skin, which leads to excoriation (Fig. 3.9), lichenification (Fig. 3.10) and, in pigmented skins, lichenoid papules (Figs 3.11 and 3.12). The epidermal barrier is disordered in eczema. This predisposes to infection, which is encouraged by scratching. Postinflammatory hypo- and hyperpigmentation are common in dark skins (Fig. 3.13) and take time to clear (Fig. 3.14).

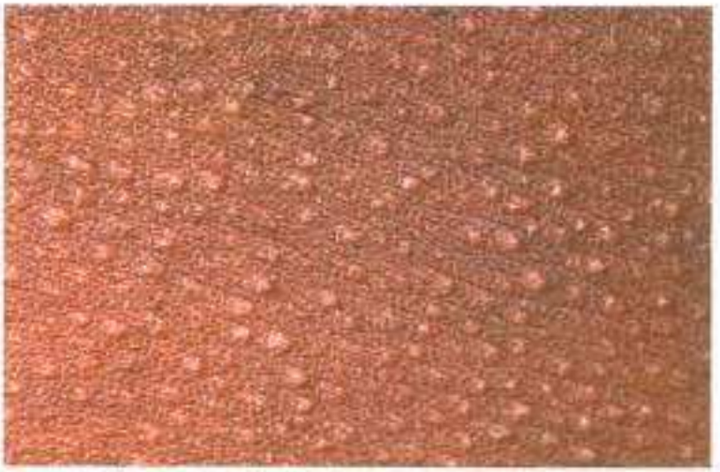


Fig. 3.8 Follicular eczema. In dark skins in particular, the eczematous papules may be centred around hair follicles.

Fig. 3.9 Excoriated eczema. Eczema is very itchy and some patients excoriate the skin and induce bleeding as a result.

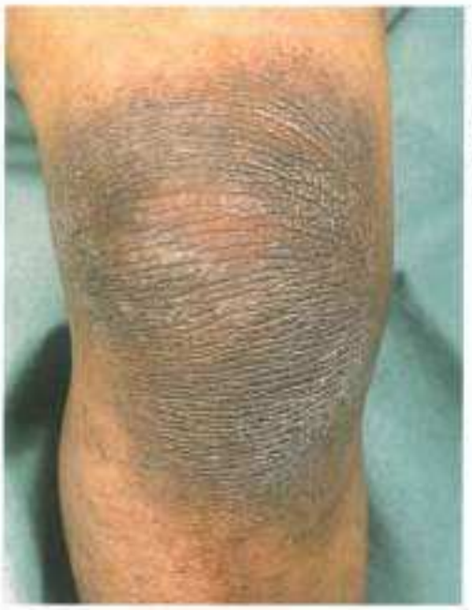


Fig. 3.10 Lichenification. The skin is thickened and the creases prominent. Hyperpigmentation is common in dark-skinned races. This child has atopic eczema.

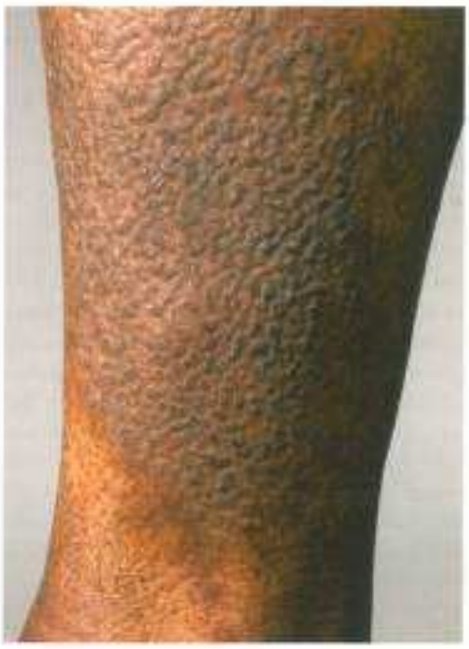


Fig. 3.11 Lichenoid eczema. There is a plaque consisting of hyperpigmented thickened papules. It was well defined and unilateral and due to lichen simplex.

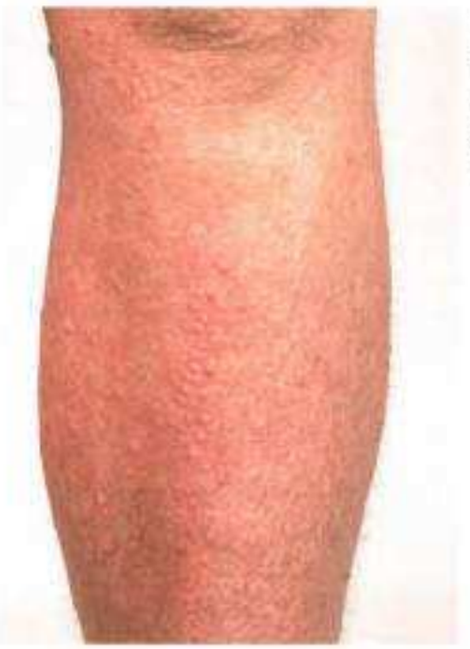
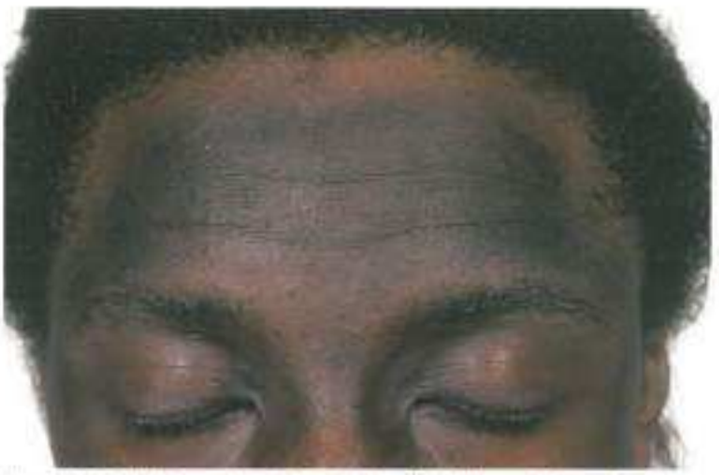
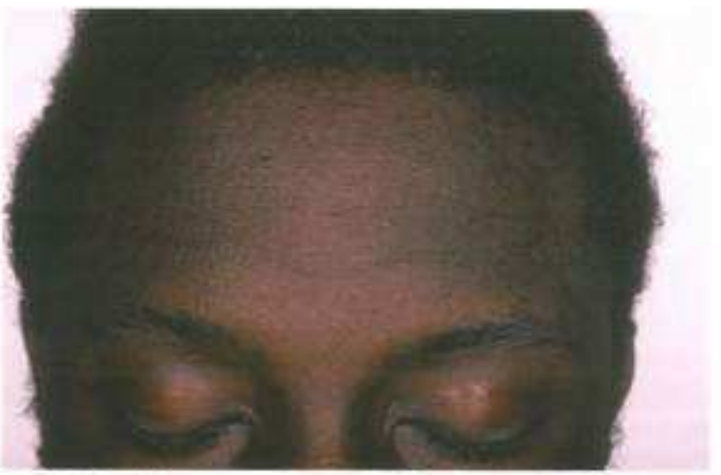


Fig. 3.12 Lichenoid eczema. Although not as common, lichenoid papules may also occur in Caucasian skin from scratching and rubbing the eczema.



Figs 3.13 Postinflammatory pigmentation. Postinflammatory hyperpigmentation (and hypopigmentation) following eczema is common in pigmented skins.



Figs 3.14 Postinflammatory pigmentation. The pigmentation is disfiguring and may take some years (in this case [Fig. 3.13], three) to clear spontaneously.

Atopic dermatitis (atopic eczema)

A common chronic but eventually self-limiting pruritic inflammatory disorder, mainly of childhood, but sometimes persisting into adult life (Fig. 3.15). It is punctuated by relapses and remissions, is genetically determined and associated with other atopic disorders.

Aetiology

Atopic dermatitis predominately affects infants and children although it may persist into or reappear in adult life. It occurs in all races and most have a personal or family history of atopy with over half developing asthma, allergic rhinitis or urticaria. These disorders are inherited as autosomal dominants with incomplete penetrance. Atopic dermatitis is much more common in monozygotic than in dizygotic twins who have the same risk as anyone else. The prevalence of eczema, asthma and positive prick tests has increased since the early 1970s, and this may be owing to environmental rather than genetic factors. The disorder has become more common in the middle classes and it is suggested that the indoor environment of central heating and better insulation increases the exposure of children to house dust mites. It is more common in migrants, for example in black Afro-Caribbeans born in London than in those born and raised in Jamaica, and this may be an effect of the cooler, less humid environment of the UK.

There is evidence of immunoaberration. In 80% there are findings of eosinophilia, raised IgE levels, positive respiratory allergens and increased transepidermal water loss and reduced surface hydration. These cases are said to have 'external disease'. The rest are predominantly female, have normal IgE levels and late onset relatively mild 'intrinsic' disease. Increased palmar linearity, keratosis pilaris and pityriasis alba are associated with the former and Dennie-Morgan infraorbital folds with the latter.

Other common findings are decreased delayed hypersensitivity responses, increased susceptibility to viral and bacterial infections, white dermographism and xerosis (dryness). The most important finding in recent times, however, is that of mutations in the filaggrin gene which may be responsible for the impairment of the function of the stratum corneum. This may permit permeation of environmental allergens and therefore exposure of immunocompetent cells to them leading to an immunological response of IgE and T cells.

Filaggrin is found within the epidermal diffentiation complex (EDC) on chromosome 1q21. These are a cluster of genes and gene families which encode proteins involved in the terminal differentiation of the epidermis.

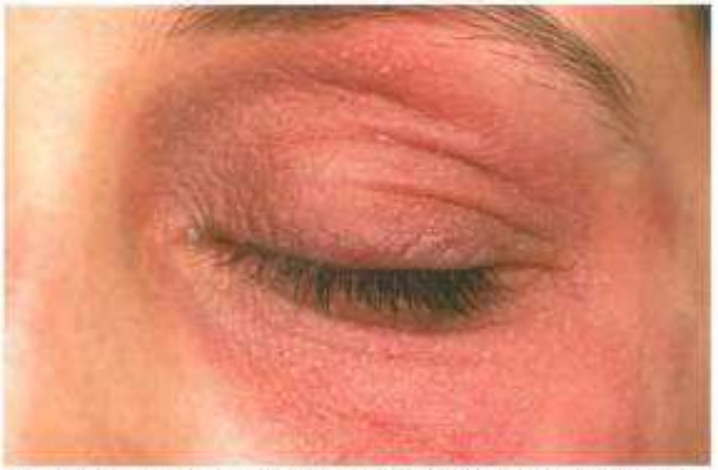


Fig. 3.15 Atopic dermatitis. Eczema is itchy and rubbing of the skin results in pronounced lichenification, particularly of the flexures, including the eyelids.

The main function of filaggrin is to aggregate keratin filaments resulting in keratinocyte compaction and formation of the stratum corneum. It is the only gene so far established as being associated with atopic dermatitis.

T lymphocytes are the major cells infiltrating the skin in atopic dermatitis. Langerhans and other dendritic antigen presenting cells interact with the external and autoallergens and produce a predominantly TH1 cell response (producing cytokines IL-4, IL-5 and IL-13) in the acute phase and TH2 cell response (expressing IFN-γ) in chronic lesions. IL-4 and IL-13 induce B lymphocytes to undergo IgE production. IL-5 together with granulocyte macrophage colony stimulating factor from lesional keratinocytes are essential for the differentiation, activation and survival of eosinophils.

After stroking normal skin, erythema and oedema (wheal and flare) occurs, but stroking atopic skin results only in a white line. The skin also appears generally pale. The significance of this abnormal tendency to vasoconstriction is not explained, but some believe that there is an impaired β-adrenergic response leading to excessive α-adrenergic stimulation, comparable perhaps to a similar mechanism in asthma. A delayed blanch phenomenon with acetylcholine is quite specific for atopic dermatitis but not so for other manifestations of atopy; the sweat glands are more responsive to acetylcholine in atopic dermatitis, possibly corresponding with the observation that increased sweating makes atopic dermatitis worse.

Eosinophilia is noted in those with severe dermatitis with a personal history of respiratory disease but not in those without. Eosinophilic remnants are found in the early inflammatory infiltrate and may play an important role.

Mast cells have been considered important in atopic dermatitis, particularly because they are very relevant to allergic rhinitis, which so often accompanies atopic dermatitis. On the one hand, IgE antibodies are raised in 80% of patients and prick tests are positive to a number of environmental allergens; on the other hand, 20% of patients with atopic dermatitis have normal IgE levels and negative skin tests, which is perplexing. Mast cells are found in just as high numbers as in psoriasis or lichen planus, and antihistamines have no effect when given alone. The raised IgE levels may relate to respiratory atopy, for levels are most commonly normal in atopics who have dermatitis alone. It is also confusing that atopic dermatitis occurs in X-linked agammaglobulinaemia where IgE levels are clearly minimal or non-existent, and eczema is not described in conditions where IgE levels are high. Raised IgE levels may, therefore, be an epiphenomenon related to respiratory disease. Genetic linkage studies have revealed a gene that encodes a variant of the β-subunit of the high-affinity IgE receptor, which leads to the release of proinflammatory mediators by mast cells, but this linkage is not found in atopic individuals.

Epicutaneous patch tests with aero allergens may induce eczematous lesions, for example to house dust mite, but they may also be positive in atopic individuals without dermatitis. Environmental manipulation by treating carpets with an acaricidal foam and powder and covering mattresses gives varied results. The theory is that the allergen binds to IgE on Langerhans' cells and results in the release of proinflammatory mediators and facilitates antigen presentation to $CD4^+$ T lymphocytes. The activated T cells express a TH2 phenotype and elaborate cytokines such as interleukins (IL) 4 and 5 but little interferon-gamma. IL-4 causes increased IgE production from B cells and upregulates CD23 expression on Langerhans' cells. IL-5 is thought to contribute to local tissue damage by attracting and activating eosinophils.

Patients with atopic dermatitis have a decreased incidence of sensitivity to contact allergens, for example in North America to the common plant allergen poison oak (*Rhus diversiloba*). Skin test responses to candidal and streptococcal antigens and in-vitro lymphocyte transformation responses to these and other mitogens are reduced. Nonetheless, these abnormalities may return to normal during remissions of the disease. It is suggested, therefore, that there is a reversal block in the cutaneous expression of delayed

hypersensitivity. In view of the immediate hypersensitivity reactions (raised IgE, positive prick tests to food and aero allergens and raised histamine levels), it is proposed that histamine release via these IgE-mediated responses may interfere with cell-mediated immunity through inhibition of histamine H_2 receptor-bearing lymphocytes. Alternatively, or in addition, IgE immune complexes may inhibit cell-mediated immunity by blocking lymphocyte proliferation responses to antigen. This defective cell-mediated immunity could allow increased IgE production, permitting a vicious circle. Therefore, skin patch tests are usually, but not always, negative in atopic dermatitis, and in particular some patients sensitize to their topical medicaments.

Atopics have a reduced ability to produce a cell-mediated response and are more susceptible to vaccinia, herpes simplex and molluscum contagiosum viruses. Prior to the eradication of smallpox, children with atopic dermatitis were never vaccinated because of the high risk of generalized vaccinia. Eczema herpeticum remains a very real problem and children with molluscum contagiosum are almost always atopic. An infective dermatitis associated with human T cell lymphotrophic virus type 1 (HTLV-1) in Jamaican children, who suffer an exudative and crusted eczema, particularly around the ears, nostrils and scalp, is now well recognized in association with this virus.

Staphylococcal and streptococcal infections are common, and 90% of patients are densely colonized with *Staphylococcus aureus*, although overt infection may not be present. The severity of eczema is proportional to the colonization with *S. aureus* and appropriate antibiotics have beneficial effects. Half of these *S. aureus* strains secrete toxins, particularly staphylococcal enterotoxins and in particular toxic shock syndrome toxin 1 (TSST-1). Applications of the staphylococcal enterotoxins to the normal skin of patients with atopic dermatitis does produce erythema and induration. The supra-antigenic activity of *S. aureus* exotoxins may be important. Superantigens can bind to class II major histocompatibility complex (MHC) molecules on epidermal Langerhans' cells, macrophages and monocytes, resulting in the release of proinflammatory mediators such as IL-1 and tumour necrosis factor alpha. In addition, they can interact with the T cell receptor in a very specific way. Whereas conventional antigens require recognition of all five elements of the T cell receptor, the recognition sequence of superantigens is almost entirely dependent on Vβ only; this leads to activation of a significant percentage of the entire T cell population and, consequently, to massive cytokine production and inflammation. Activated keratinocytes (as opposed to normal keratinocytes) express MHC class II complex and, therefore, can function as superantigen-presenting cells to neighbouring T cells. Since the release of cytokines further activates keratinocytes, a self-perpetuating cycle ensues.

Dietary deficiency of essential fatty acid produces severe abnormalities of the skin in experimental animals. In eczema, the two main dietary essential fatty acids, linoleic acid and α-linoleic acid, are normal but their metabolites are reduced, suggesting a possible impairment of essential fatty acid metabolism at the Δ6-desaturase level. Oral treatment with evening primrose oil, which contains γ-linoleic acid, produces some clinical improvement in some patients.

Clinical Features

Symptoms

An itchy rash, usually beginning at about 3 months of age (Fig. 3.16).

Morphology

The rash is strikingly symmetrical. There is an ill-defined redness and fine scaling, together with serous exudation, vesiculation and crusting in the more acute states. The skin is generally dry or xerotic.

Distribution

The condition starts on the face and spreads to the trunk and limbs (Fig. 3.17). The flexures are especially affected: in particular, the eyelids, neck,

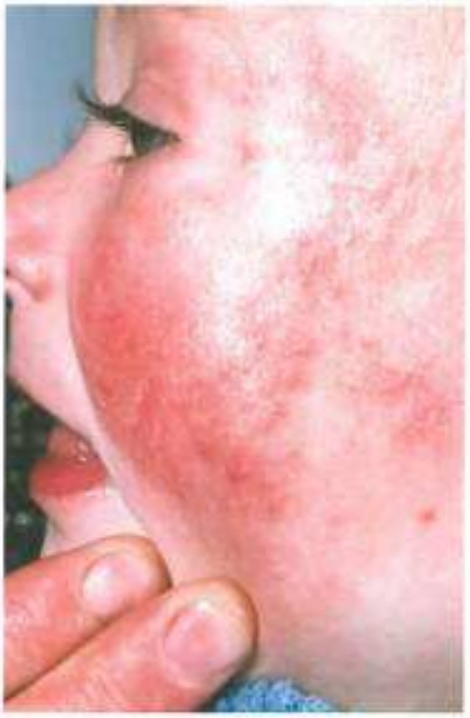


Fig. 3.16 Atopic dermatitis. The disorder usually starts on the face, classically at 3 months. The eczema is subacute on this infant's cheeks.

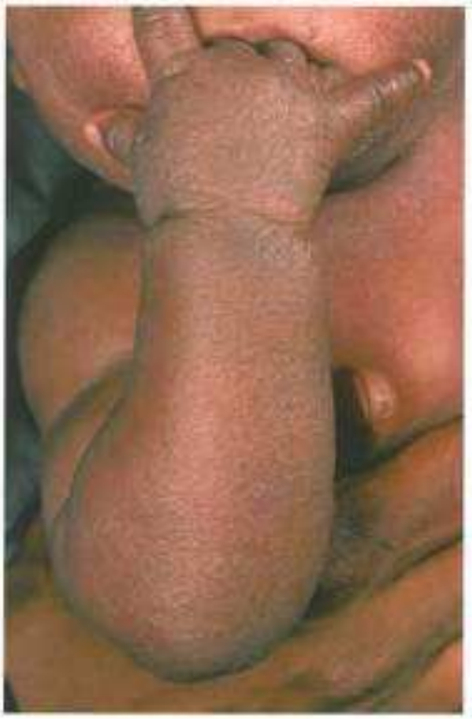


Fig. 3.17 Atopic dermatitis. The eczema spreads in infancy from the face to limbs with particular involvement of the flexures.

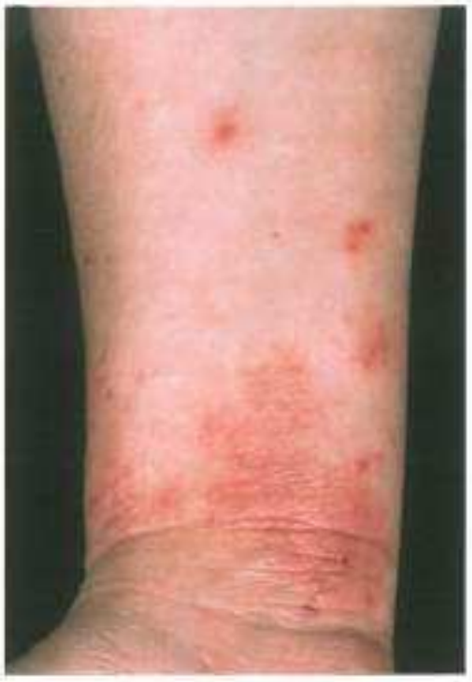


Fig. 3.18 Atopic dermatitis. The limbs are commonly affected, particularly the flexures with lichenification as here at the wrist.

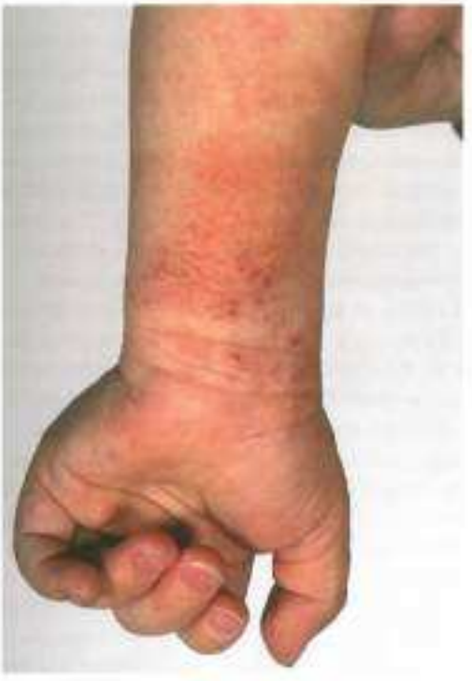


Fig. 3.19 Atopic dermatitis. There is an ill-defined red, scaly and excoriated eruption at the wrists.

elbows, ankles, posterior gluteal folds, wrists, (Figs 3.18 and 3.19) and knees (Figs 3.20 and 3.21). In severe cases, most of the body is involved (Fig. 3.22). In Afro-Caribbean infants, the eczema and rubbing may result in a temporary loss of scalp hair (Fig. 3.23). Occasionally in children, the eczema predominates around the lips, a cheilitis that is often perpetuated by licking of the lips (Fig. 3.24). In adults, the areolae of the breasts and adjacent skin may be affected (Fig. 3.25). An infra-orbital fold described by Morgan is said to be characteristic of the atopic individual in Caucasians.

Complications of Atopic Eczema

Pruritus and pigmentation

Atopic eczema is very itchy, and excoriations and lichenification result from scratching and rubbing. The degree of scratching varies but in some cases excoriations, with consequent pigmentary abnormalities and occasionally scarring, may dominate the physical signs, overshadowing the eczematous changes. The condition is then sometimes known as *Besnier's prurigo* (Fig. 3.26). Postinflammatory hypo- or hyperpigmentation is common in dark skins; in many Caucasians a characteristic reticulate pigmentation occurs around the neck (Fig. 3.27).

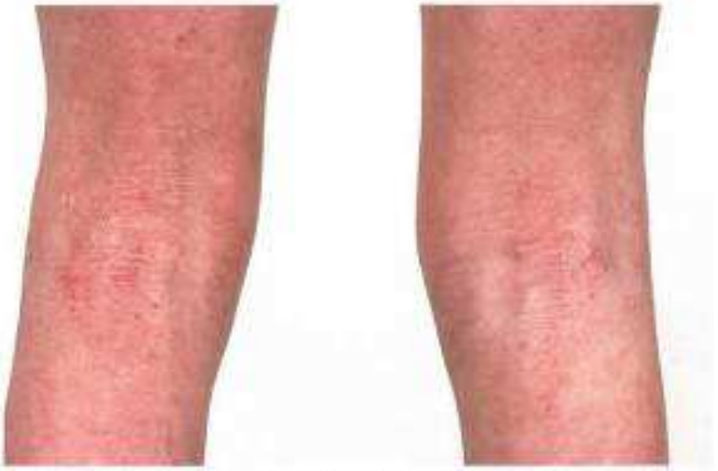


Fig. 3.20 Atopic dermatitis. Involvement of the flexures is characteristic of eczema. Lichenification is usually pronounced.

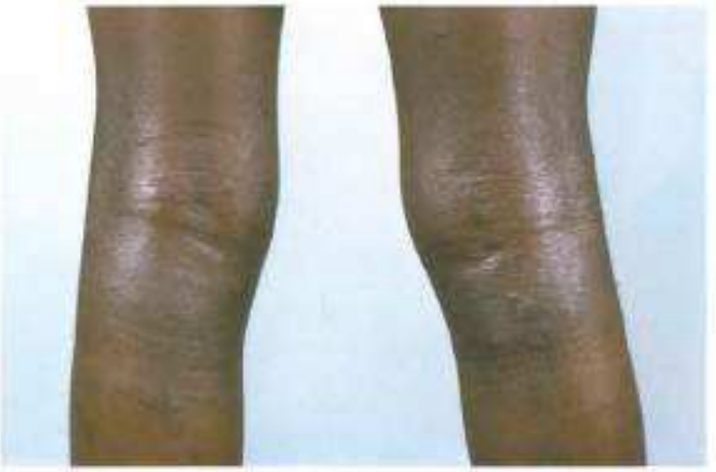


Fig. 3.21 Atopic dermatitis. The erythema of eczema is less marked in black skin, which makes the diagnosis more difficult in comparison to that of Figure 3.20 but the lichenification is obvious.

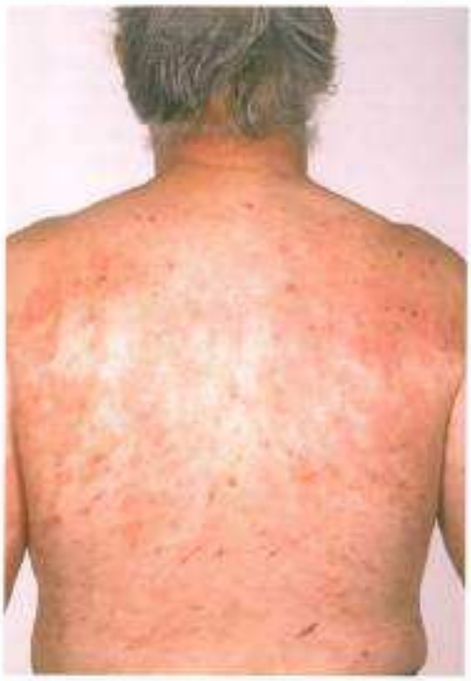


Fig. 3.22 Atopic dermatitis. Eczema may become extensive, even erythrodermic. In adults there is usually some precipitating factor such as alcohol misuse.

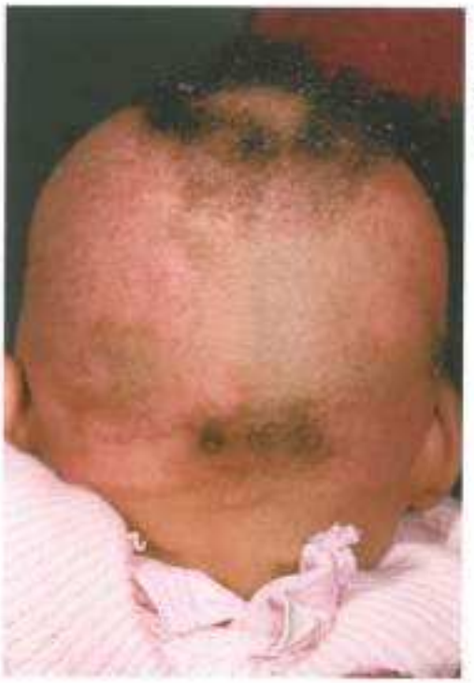


Fig. 3.23 Atopic dermatitis and hair loss. In Afro-Caribbeans, eczema in the scalp may lead to a temporary loss of hair.

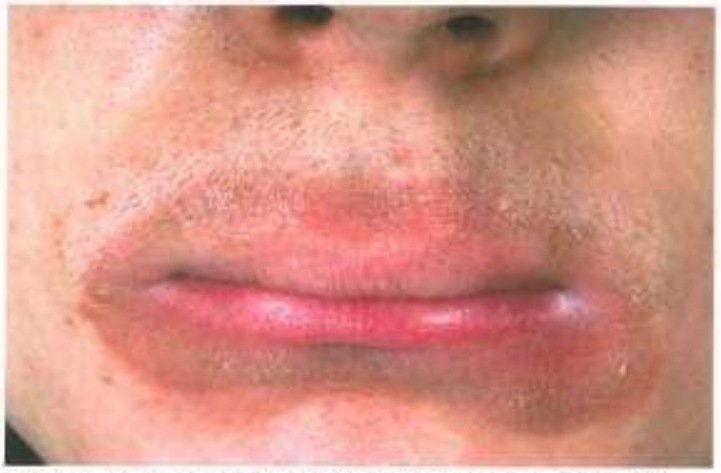


Fig. 3.24 Lip licking. The eczema may be pronounced around the mouth in children, who get into the habit of licking around the lips.

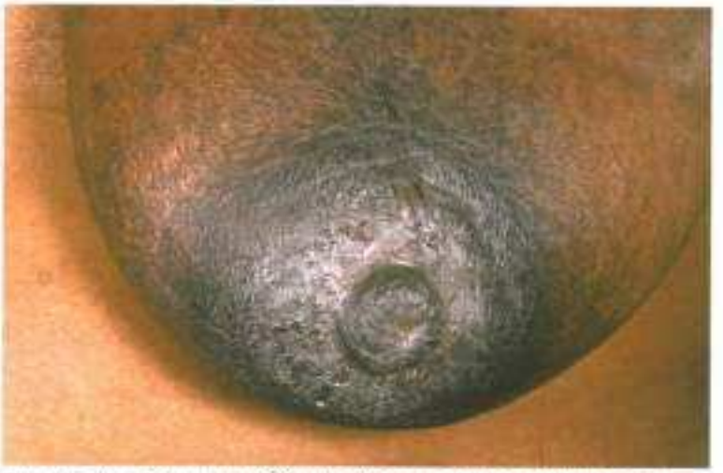


Fig. 3.25 Atopic dermatitis. Occasionally eczema may be most troublesome on and around the areola of the breast, particularly in African-Americans or Afro-Caribbeans.

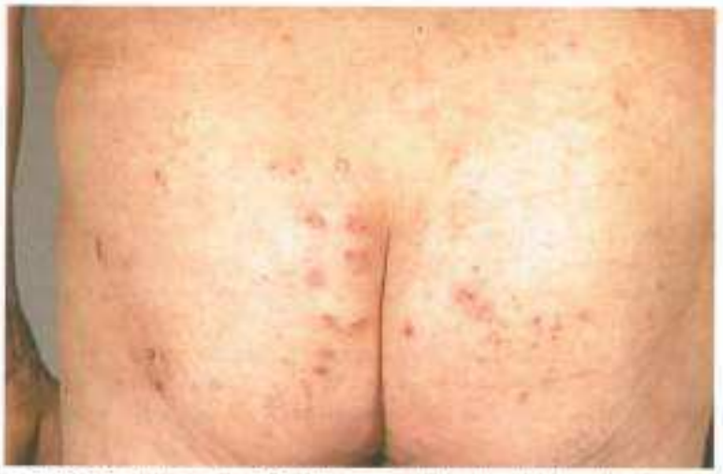


Fig. 3.26 Besnier's prurigo. Sometimes excoriations dominate the clinical picture, with very little evidence of active eczema.

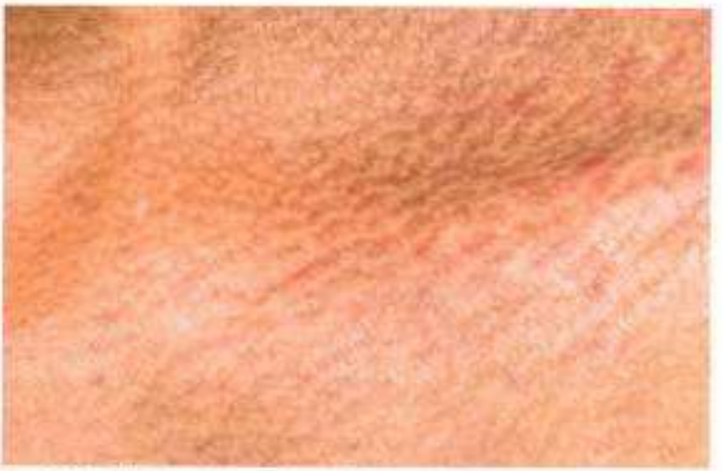


Fig. 3.27 Reticulate pigmentation of the neck. In chronic atopics, a curious unexplained rippled and reticulate hyperpigmentation occurs around the neck.

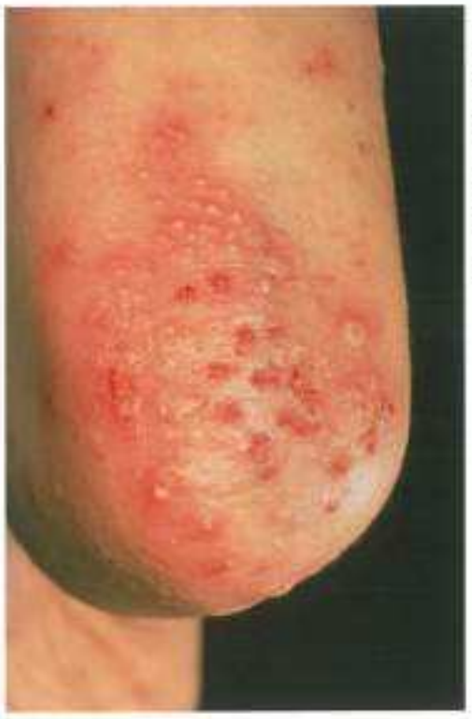


Fig. 3.28 Infected eczema. Yellow pustules are present superimposed on the eczema. *S. aureus* and released exotoxins may penetrate the stratum corneum more easily because of a skin barrier defect due to mutations in the filaggrin gene.

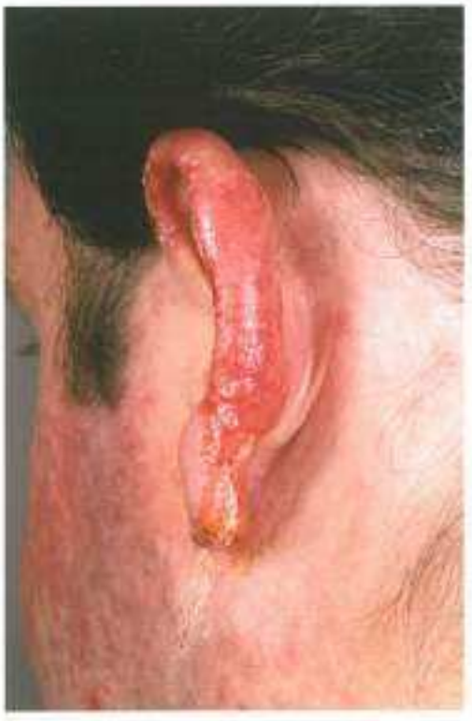


Fig. 3.29 Infected eczema. There is erythema, oedema and weeping of the skin, which has become purulent and infected in an acute eczema.

Bacterial sepsis

Particularly in its acute or subacute stages, eczema frequently becomes secondarily infected. It can be studded with yellow pustules (Fig. 3.28), oozing yellow purulent material (Fig. 3.29), or covered with yellow crusts (Fig. 3.30), when it is described as *impetiginized eczema*.

Molluscum contagiosum

The atopic patient is more prone to infection with the pox virus that causes molluscum contagiosum (Fig. 3.31). It is frequently not recognized by the patient, or sometimes by the practitioner (particularly because eczema often develops around individual mollusca); consequently, the patient applies topical steroids to the infection, mistaking it for eczema, and as a result the virus flourishes unrestrained.

Kaposi's varicelliform eruption

This is an important, serious, secondary infection of atopic eczema with either vaccinia or herpes simplex, which can occur even in patients whose eczema is in remission. Nowadays only herpes simplex infections (eczema herpeticum) are a problem. The virus colonizes eczematous and non-eczematous skin and leads to a widespread eruption (Fig. 3.32) of discrete, tense vesicles (Fig. 3.33) and vesiculopustules (Fig. 3.34) surrounded by erythema. Secondary bacterial colonization may occur (Fig 3.35). This is coupled with a viraemia. The patient may be extremely ill, with multisystem (including central nervous) involvement. The use of systemic acyclovir is mandatory and usually life saving. An atopic subject should be advised to avoid contact with individuals with an active herpes simplex infection.

Infective dermatitis associated with HTLV-1

Sweet in 1966 described a pattern of eczema in Jamaican children where exudation and crusting predominated; it occurred particularly around the nostrils, ears and scalp and eventually could become generalized with a fine papular rash. Although it responded to topical steroids and antibiotics, it always appeared to relapse. It is associated with HTLV-1 (human T cell lymphotropic virus 1). This virus clusters in the Caribbean, Southern Japan, Central Africa and South America and is transmitted parenterally, sexually or from mother to child. It may very occasionally, after a long latent period, result in adult T cell leukaemia/lymphoma or a myelopathy known as *tropical spastic paraparesis*. This infective dermatitis is being described in the other countries where the virus is endemic, and additional involvement of the axillae and groin and neck with a chronic watery nasal discharge without signs of rhinitis have been added to the clinical description. The condition appears to be recalcitrant, is associated with HTLV-1 antibodies and staphylococci or streptococci are isolated from the lesions and from the anterior nares. There is sometimes a generalized lymphadenopathy.

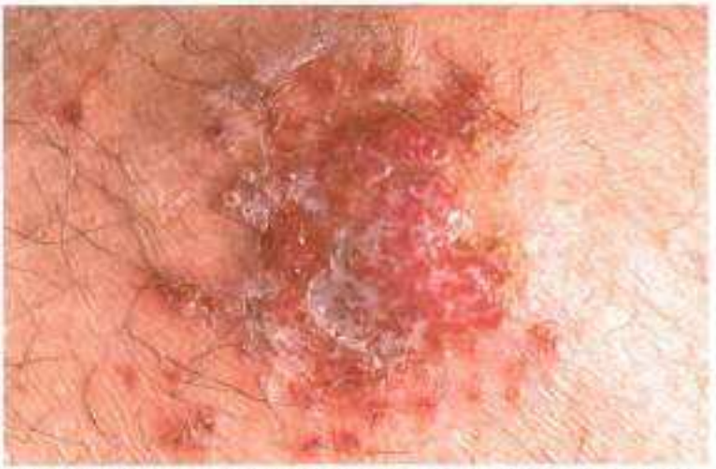


Fig. 3.30 Septic eczema. The epidermis is disrupted in eczema and secondary bacterial sepsis, manifest as a yellow purulent exudate with crusting, may occur.

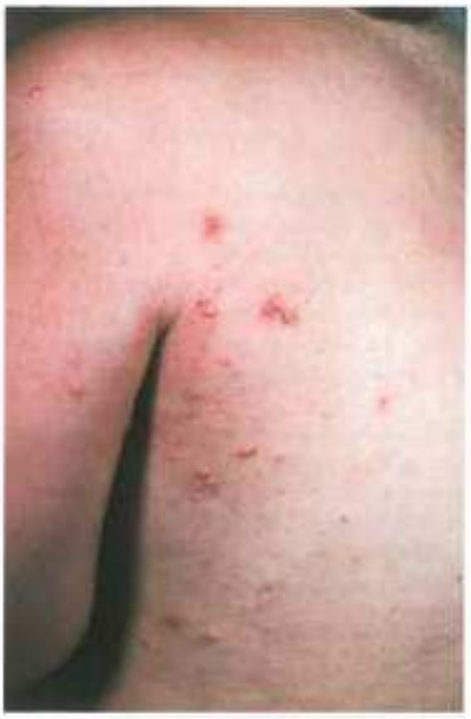


Fig. 3.31 Eczema and molluscа contagiosa. Atopics are prone to infection with certain viruses. Flesh-coloured papules of molluscа are present. Patches of eczema are also usually visible.

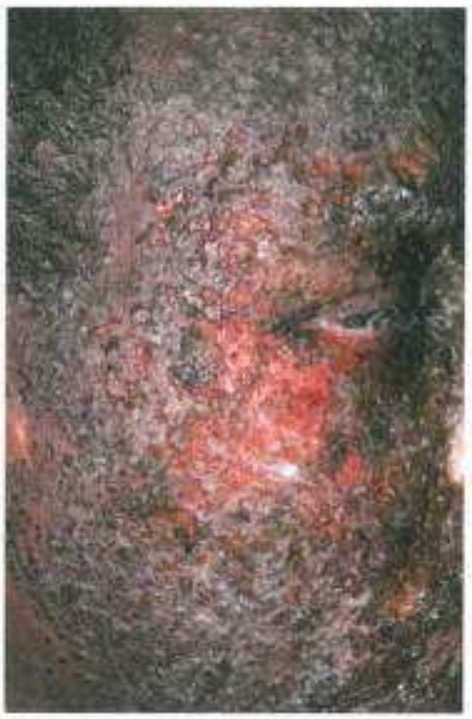


Fig. 3.32 Kaposi's varicelliform eruption. Widespread infection with herpes simplex occurs and the patient is systemically unwell. Urgent treatment with acyclovir or a derivative (if cultures show resistance) is required.

Wiskott–Aldrich syndrome

This syndrome is a rare disorder in which eczema (essentially indistinguishable from that of atopic eczema) is an important part of the syndrome. There is, however, thrombocytopenia, which is often misdiagnosed as idiopathic but does not respond to the usual treatments for that disorder (i.e. splenectomy, gammaglobulins or steroids). The Wiskott–Aldrich syndrome should be considered in all male infants with thrombocytopenia. There is purpura and excessive bleeding from excoriations in addition to the eczema. Epistaxis, bloody diarrhoea and a tendency to intracranial haemorrhage are other features. Bacterial infections (otitis media, pneumococcal pneumonia, meningitis, skin sepsis and septicaemia) and viral disorders (herpes simplex, measles and cytomegalovirus) are common, particularly if a splenectomy has been performed. The bleeding tendency is exacerbated during these infections. The children are particularly prone to autoimmune phenomena and to develop lymphomas and leukaemias.

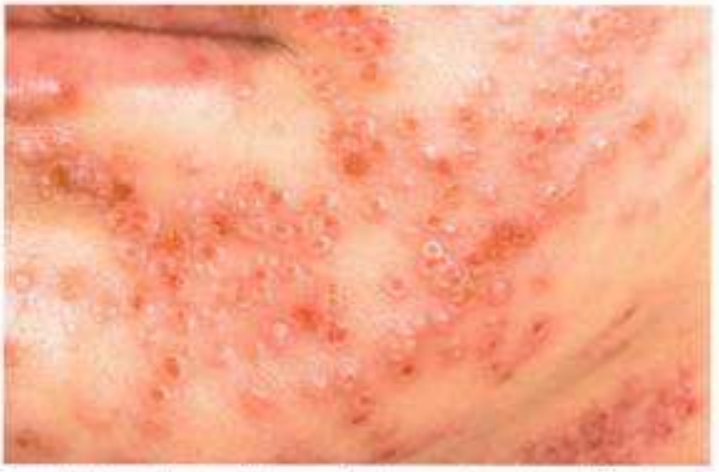


Fig. 3.33 Kaposi's varicelliform eruption (eczema herpeticum). Discrete umbilicated vesicles surrounded by erythema are present.

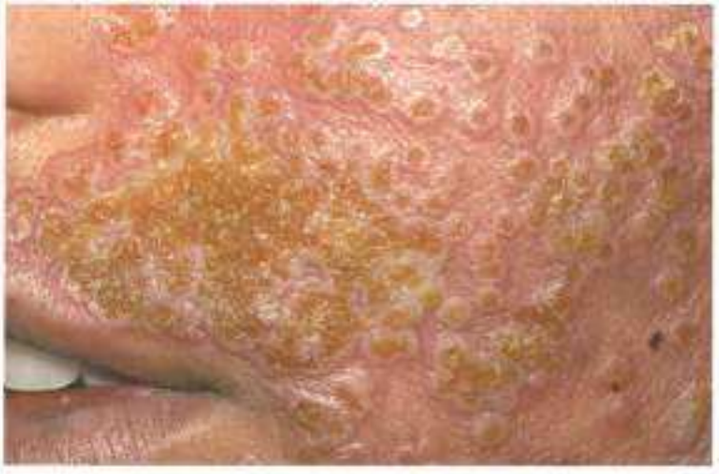


Fig. 3.34 Kaposi's varicelliform eruption. The lesions may become purulent and simulate impetigo. The umbilicated vesicles are, however, characteristic.

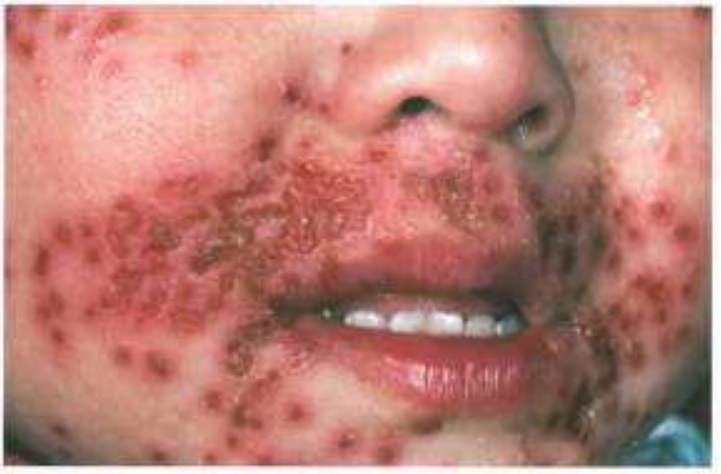


Fig. 3.35 Kaposi's varicelliform eruption. This may occur in the very young and be mistaken for impetigo when secondary bacterial infection occurs.

The disorder is transmitted as an X-linked recessive trait and the gene has been mapped to Xp 11.22, which encodes for the *WAS* protein which controls the assembly of actin filaments which are required for platelet, T cell and antigen presenting cell function.

Job's syndrome

This is eczema associated with eosinophilia and hyper-IgE, recurrent infections and bony changes, giving rise to coarse facies, hypertelorism, hyperostosis frontalis externa, scoliosis and osteoporosis. Primary teeth are retained. Secondaries fail to erupt. There is abnormal neutrophil chemotaxis due to reduced production of γ interferon. The patient is reasonably well but gets recurrent 'cold' abscesses particularly of the skin and lungs but also of other organs. Recurrent pneumonia and bronchopleural fistulae and cysts may result in restrictive lung disease. Mucocutaneous candidiasis and staphylococcal infections are most frequently involved. It is usually inherited as autosomal dominant with variable penetrance. Job's syndrome is a subset of hyperimmunoglobulin E syndrome, where there are heterogeneous mutations in the gene encoding Signal Transducer and Activator of Transcription 3 (STAT3), which is critical to the signalling pathways of IL-6 (which promotes acute phase responses) and IL-10 (an anti-inflammatory cytokine), thus explaining the 'cold abscesses' and destructive inflammatory responses, particularly in the lungs. The high levels of IgE would suggest a diagnosis in an eczematous subject with recurrent infections. Long-term prophylactic antibiotics are given as treatment.

Differential Diagnosis

Infancy and Childhood

- Seborrhoeic eczema
  The distinction between this and atopic dermatitis is not always straightforward but the onset of seborrhoeic eczema is usually at 6 weeks and lasts approximately 6 weeks. It does not itch, there is no family history of atopy and the distribution is different, affecting primarily the scalp, face, axillae and napkin areas.
- Scabies (see below)

Adult life In a patient who has never had eczema previously there are two common alternative diagnoses:

- Contact dermatitis
  It is always worth considering contact dermatitis, particularly to metal, which may affect similar sites, for example the neck (necklace or its clasp), forearms and elbows (metal strap of handbag) and wrists (watchstrap or bracelet). Patch tests would be positive in contact dermatitis but usually negative in atopic eczema.
- Scabies
  The quality of the itch is different to eczema in that it is more severe, especially at night. There may be a history of someone else itching. The finding of burrows and the identification of the acarus under the microscope will clinch the diagnosis.

Management

At present there is no cure but for the majority it resolves with time. Many children are better by the age of 2 or 3 years. More than half are completely free of the disease by 13 years of age. There may be some relapse during adolescence or early adult life, but most recover by 30 years of age. There are, however, a few who suffer from it for virtually all their lives. It is difficult to predict the prognosis, but severe disease in infancy and the involvement of the fronts of the elbows and knees often augur badly.

Since there is no specific remedy and the disease has a variety of forms and complications, treatment is not straightforward. The dryness, the eczema itself, the degree of scratching, the presence or absence of infection and the extraneous psychological and social factors all need to be assessed.

Management of the xerosis

Virtually all patients with atopic eczema have a dry skin, which remains with them all their lives. It is affected by climatic conditions and eczema is worse for most patients during winter when there is a chill factor and the relative humidity is low. Xerotic skin is also made worse by irritants, e.g. wool, water and detergents.

Attention to improving the dryness every day is critical. It is well worthwhile getting into a routine of using lubricants first thing in the morning and at bathtime. An explanation of the simple physics of the adverse effects of low temperature and low relative humidity on the skin during the winter months is important. The lubrication needs to be increased during these times. Irritants such as woollen clothing (cotton is much better), soaps and 'bubble baths' should be prohibited. It is important to dry the skin properly after a bath.

There are a variety of soap substitutes, bath additives and emollients that are available to counteract the innate dryness of eczema although they have no effect on the inflammatory process. Most are based upon emulsifying wax, liquid paraffin, white soft paraffin, lanolin and urea. In general, vehicles (inert carriers of the active ingredient) should be ointments rather than creams. They promote percutaneous absorption and have an emollient effect of their own.

Management of the eczema

Emollients only help the xerosis. Topical steroids are the most effective agents for the eczema itself.

Topical glucocorticosteroids

An understanding of topical steroids is fundamental to the management of eczema. They are highly efficacious anti-inflammatory and immunosuppressive agents. They are classified into four strengths in the UK and Europe where class I is the mildest and IV is the most potent. In the US however, there are seven strengths where class I is the most powerful and VII is the weakest.

The choice of steroid depends on the site and stage of the eczema and the age of the patient.

- **The site** Hydrocortisone is the steroid of choice for the face; 0.5% is usually ineffective so in practice 1.0 or 2.5% is needed. However, for the body and limbs, a more powerful steroid is generally required (Figs 3.36 and 3.37). Moderately potent steroids are effective for flexural sites such as the groin, where percutaneous absorption is greater because of the occlusion, and elbow and knee flexures where the skin is thinner. Frequently, it is helpful to use a potent steroid first, in order to gain control, before returning to the less powerful one.
- **The stage** The dry, red, scaly variety responds to the above measures. However for chronic lichenified eczema, powerful steroids are indicated because the skin is thickened to such an extent that weaker steroids cannot penetrate in sufficient quantity to be effective. Where excoriation predominates, bandages and sedatives are much more useful than topical steroids. If sepsis is present, oral antibiotics are required.
- **Age** Particular care should be taken in infants where absorption is increased because there is a large surface area in relation to size. Steroids such as clobetasone butyrate and fluticasone, which are broken down and not absorbed, are particularly useful for their lack of systemic toxicity.

There is a concern amongst patients or their parents about using topical steroids. Side-effects were seen frequently in the past, often due to misdiagnosis when they were prescribed for the wrong conditions (e.g. infections, rosacea or perioral or periorbital acne). In addition, inappropriate quantities of very potent steroids were prescribed for eczema and psoriasis and consequently local (Fig. 3.38) and occasionally systemic side-effects occurred. Today, side-effects of topical steroids are much less common, but a hostility to them does exist despite the fact that they represent the single most effective remedy for controlling the disease if used sensibly.

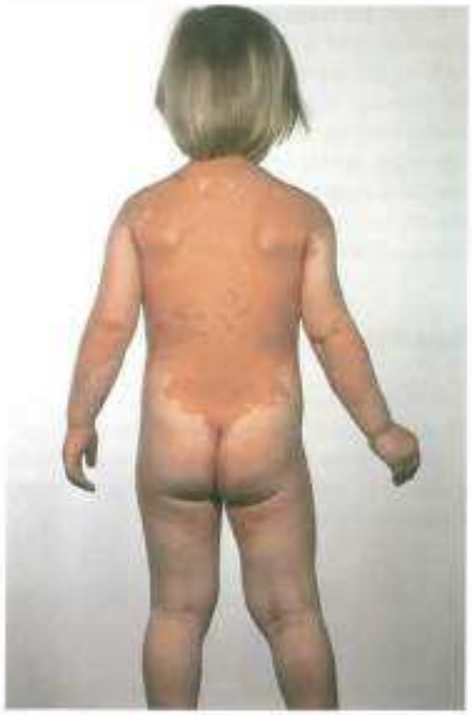


Fig. 3.36 Atopic eczema. The treatment of eczema has been revolutionized by the appropriate use of topical steroids.

Fig. 3.37 Atopic eczema treated with topical steroids. The choice of potency is important. This child (Fig. 3.36) responded to a class II steroid.

It is important to monitor how much steroid is being used and to ensure that it is applied only to the eczema and not to the normal skin. There is strong evidence that the steroid remains active in the skin for 24 hours; therefore, once daily applications are probably sufficient. Some patients tend to use steroids as lubricants, but by proper instruction in the use of emollients it is often possible to reduce the amount of steroid being applied. If more than 30 g is being used every week, the patient should be seen by a specialist and other measures considered. Systemic steroids are sometimes required for atopic eczema, but their prescription should be a specialist's decision.

Tar

Before the advent of hydrocortisone in 1952, tar was the mainstay of treatment. Its mode of action is unknown. There are various commercially available formulations including in combination with topical steroids. Bandages containing tar or ichthammol (a form of tar) are invaluable in Besnier's prurigo.

Topical calcineurin inhibitors

Tacrolimus is a macrolide lactone isolated in Tsukuba in Japan from a *Streptomyces* sp. found in soil. Tacrolimus is an acronym for Tsukuba macrolide immunosuppressive. It inhibits IL-2 gene expression in T cells and is highly effective topically in atopic dermatitis. Although it has a high molecular weight it is able to penetrate the disordered barrier in eczema without difficulty and this probably explains why it is effective topically in eczema but not in psoriasis. It is a much more powerful immunosuppressive than ciclosporin, which is not effective topically. Tacrolimus may cause a short-lived burning sensation. It is available as Protopic (0.03% and 0.1%) and as its close relative pimecrolimus 1% (Elidel).

Management of infection

Bacterial sepsis

It is known that certain toxin-producing staphylococci and streptococci function as superantigens. These are a unique group of proteins, manufactured by bacteria, that produce their clinical effect by bypassing some elements of the antigen-mediated immune response sequence, leading to much greater activation of the T cell population and thus cytokine release. *S. aureus* and released exotoxins may penetrate the skin more easily because of the impaired barrier function caused by the defect in the filaggrin gene. It is currently believed that treatment of infection is an important part of the management of eczema whether or not it is clinically apparent. For all minor degrees of sepsis, there are various proprietary medicaments that combine an antibacterial agent, usually neomycin, fucidic acid, tetracycline or a quinolone, with the appropriate strength of steroid.

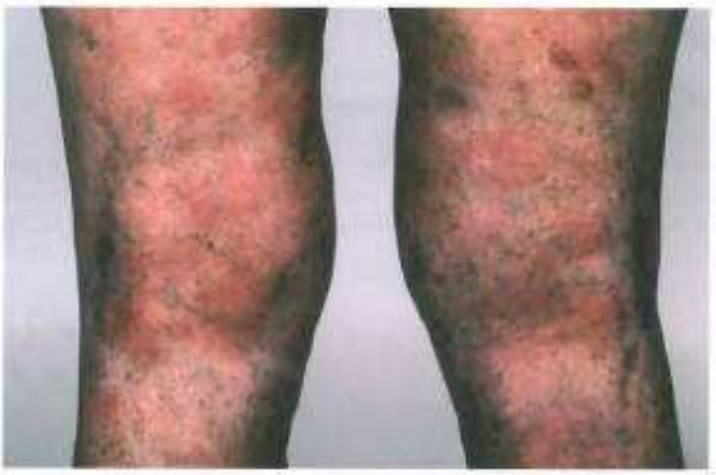


Fig. 3.38 Topical steroid misuse. Atrophy (thinning) of the skin has resulted in purpura (bruising) and visibility of the underlying blood vessels through inappropriate use of a superpotent steroid.

Although steroid–antibiotic combinations are often recommended, potent topical steroids do reduce the density of *S. aureus* in atopic dermatitis and restore the barrier function of the stratum corneum; consequently treatment with a steroid alone may still be effective. However, in more severe sepsis, where there is frank pus and yellow crusts, combined preparations and systemic antibiotics are required. Erythromycin has been the drug of

choice, since penicillin resistance is fairly common; however, erythromycin resistance is steadily increasing and flucloxacillin may be required. In these situations, particularly if they are recurrent, it is wise to take swabs from infected areas and from staphylococcal carrier sites. If these are positive, especially with increasing prevalence of community (Panton Valentine) or hospital-acquired MRSA, standard measures of staphylococcal elimination should be employed: the use of mupirocin ointment at carrier sites, chlorhexidine gluconate as a shampoo, 2% triclosan as a bath concentrate and chlorhexidine as a dusting powder. Chlorhexidine mouthwash is indicated when there is recovery of staphylococci from the throat. Swabs from carrier sites from partners of the patient may be helpful. The house is often infected and frequent changes of linen and clothing is advisable; these should be laundered at high temperatures. Materials that may harbour bacteria, such as face flannels, should be discouraged.

Molluscum contagiosum

Although cryotherapy is slightly uncomfortable, in skilled hands it can be completed quickly without unduly upsetting a child. Prior use of local anaesthetic creams (EMLA) has made this easier. Any surrounding eczema may then be treated with a steroid.

Kaposi's varicelliform eruption (Eczema herpeticum)

Acyclovir 200 mg orally, five times daily for 5 days, and 5% acyclovir cream applied topically five times daily to the lesion is effective. If there is any systemic complication, the drug should be given intravenously. Resistance is unusual but famciclovir is indicated if response is slow. Kaposi's varicelliform eruption has been seen in patients using Chinese herbal remedies orally (probably because of an immunosuppressive effect) and so-called herbal creams, which on subsequent testing have turned out to contain potent steroids.

Management of excoriated eczema

Acute episodes of scratching of the skin leading to multiple excoriations may be precipitated by an emotional crisis or a physical illness. In this situation, topical steroids do not work well on their own, but the use of *occlusive bandages on the limbs is helpful*, with a weak or moderately potent topical steroid being applied first (Figs 3.39 and 3.40). The bandages either contain tar (coal tar and zinc paste bandages), ichthammol and zinc and calamine or they contain zinc, calamine and clioquinol. These bandages are left on for 2 to 3 days and just a few applications can make an enormous difference to the eczema. The 'wet-wrap' technique is also useful in children. Two layers of absorbent tubular bandage are used. The inner layer is pre-soaked in warm water and the outer layer is dry. Hydrocortisone ointment (1%), or sometimes a moderately potent steroid, is applied to the skin before the wet wraps. These are very useful measures in the outpatient setting. The practice nurse can apply the bandages and instruct the parents how to use them.

Other aspects of management

Antihistamines

Sedative antihistamines are useful adjuncts to therapy. They are well tolerated by children, who may be given adult doses. At night, phenothiazine antihistamines may be given to children and hydroxyzine hydrochloride (which has anxiolytic activity) to anxious adults. During the day, less sedative antihistamines are more useful.

Diet

Although food allergy occurs, it is not reliably reproducible. Prick testing and RAST (radioallergosorbent testing) correspond in over half of patients but only a quarter have a reaction when challenged. Skin tests can remain strongly positive even after tolerance has developed, and double-blind placebo-controlled food challenges do not seem to be a benefit in most patients with mild or moderate dermatitis; even when it is, total clearance and long-term benefit is unusual. Allergen avoidance (dairy products, eggs, fish and nuts) by mothers during gestation (plus prolonged breast feeding and delayed introduction of solids) may reduce the onset of eczema during the first year but seems to have no effect on the cumulative prevalence of atopic dermatitis by the end of the second year.

Elimination diets are tedious and not very gratifying and compliance is poor. Dietary manipulations ranging from the oligoallergen approach of Atherton (avoid eggs and milk only) to those who use an antigen-free diet (Vivasorb) should be supervised by a dietitian because there is a danger of inducing malnutrition including rickets in children through restriction of vital vitamins, protein and calcium.

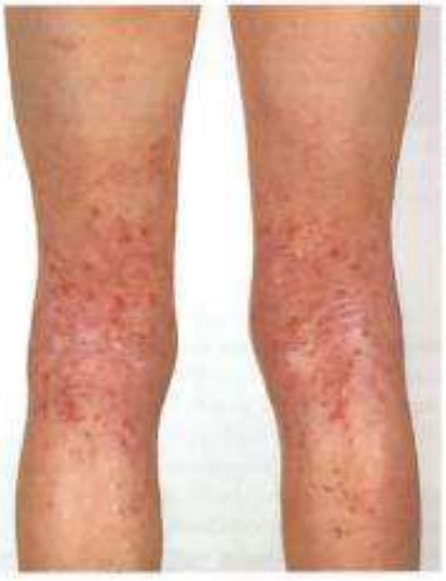


Fig. 3.39 Atopic eczema. The eruption is symmetrical, usually affecting the flexures. Scratching results in excoriations and lichenification.

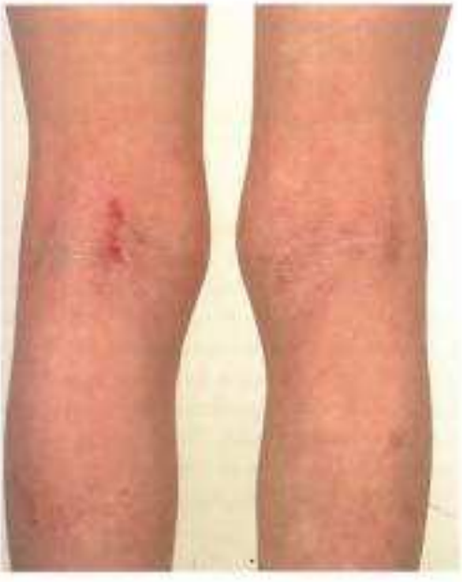


Fig. 3.40 Atopic eczema. It responds well to topical steriods but if excoriations predominate appropriate bandaging may be more effective (see Fig. 3.41).

Bedding covers

Bedding covers have been made available commercially in an attempt to isolate the patient from potential allergens in the mattress.

Day care and hospitalization

Most patients recover in hospital, often without any particular change in management or diet. Recovery may be through good nursing, removal from an allergic environment at home (house dust) or removal from psychological stress at home. It is to be avoided in children but is often of great help to adults. Access to hospital beds is much more difficult than it was previously and it is expensive; consequently day care centres for the management of skin diseases have become very useful substitutes. Applications of ointments and bandages by trained dermatological nurses are invaluable (Fig. 3.41), and the nursing support is of immense psychological benefit to the patient.

Fig. 3.41 Bandaging of eczema. Application of tube gauze bandages combined with topical steroid therapy takes time and skill but is invaluable in the management of eczema.

Mites

There are increased specific IgE antibodies to house dust mites in most patients. Patch tests with mites do produce eczema and mite allergens are found bound to Langerhans' cells and Fc-specific T cells. Increased numbers of mites are found in the homes of patients with atopic dermatitis, and there is often a marked improvement after eradication of mite allergens using various chemicals and vacuuming techniques or after removal of the patient to an allergen-free environment.

Phototherapy

Many patients notice that their eczema improves in the summer, although this may be because of increases in relative humidity. The use of narrow band ultraviolet B and also psoralen plus ultraviolet A (PUVA) has been explored in atopic eczema. It is helpful in some patients but not in all. Phototherapy is probably immunosuppressive and reduces the number of antigen-presenting Langerhans' cells. There is some disquiet about the use of PUVA in young children in view of the risks of cutaneous carcinogenesis in the long term.

Systemic agents

If topical therapy fails, systemic agents should be considered. Steroids are rarely used for long-term management but may be useful for acute exacerbations or to gain control until slower acting long-term agents such as azathioprine or methotrexate take effect. Ciclosporin does act swiftly in doses of 2.5–5 mg/kg daily. It is a potent inhibitor of T helper cell proliferation but there are significant risks of adverse effects and drug interactions.

Psychological aspects

All aspects of the art of medical practice are required to treat atopic eczema. Explanation, reassurance, sympathy, interest and encouragement are vital so that the patient and parents can build up a trust in the physician, particularly as the condition is chronic and is prone to exacerbations. Nevertheless, at times, more specialized psychological help is necessary and techniques designed to break the itch–scratch cycle have proved quite successful.

Infantile seborrhoeic dermatitis

A common self-limiting inflammatory condition occurring within the first few weeks of life, affecting primarily the scalp, face, axillae and napkin area.

Aetiology

The cause is unknown. It is a separate entity from adult seborrhoeic eczema, although its distribution is similar. It does not lead to the adult form. It was named seborrhoeic because the scales are yellow and greasy, particularly on the scalp, and sebaceous gland activity is increased.

It is not genetic nor is it caused by failure to care for the skin properly, since the mother may have several children before bearing one who develops seborrhoeic eczema. Some authorities question whether there is a nutritional element to the disorder. This is based on a report of an increased incidence in Czechoslovakia during a national food shortage. It has also been described in breast-fed infants of malnourished mothers, where the condition improved if the mothers or babies were given injections of biotin.

An allergic reaction to candidal allergens has been proposed but not substantiated. Others suggest that *Pityrosporum ovale* and *Staphylococcus aureus* are the dominant organisms, but they may be secondary invaders.

Clinical Features

Symptoms

Cradle cap or nappy rash.

Morphology

The lesions are eczematous. They are pink with a fine scale and are ill defined. Yellow crusts occur, particularly in the scalp (Fig. 3.42), around the eyebrows and ears (Fig. 3.43).

Distribution

Having started in the scalp or napkin area at around 6 weeks, the eruption spreads to the face, under the neck, the axillae (Fig. 3.44) and in some cases the body (Fig. 3.45).

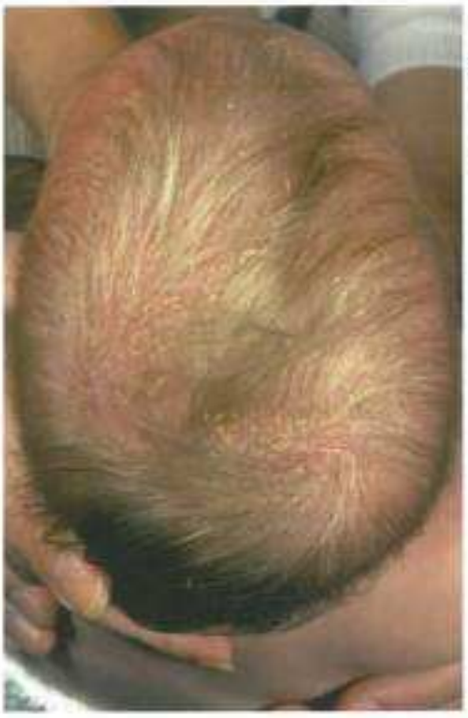


Fig. 3.42 Seborrhoeic eczema. It starts at about 6 weeks of age, earlier than atopic eczema. It is most commonly expressed as cradle cap.

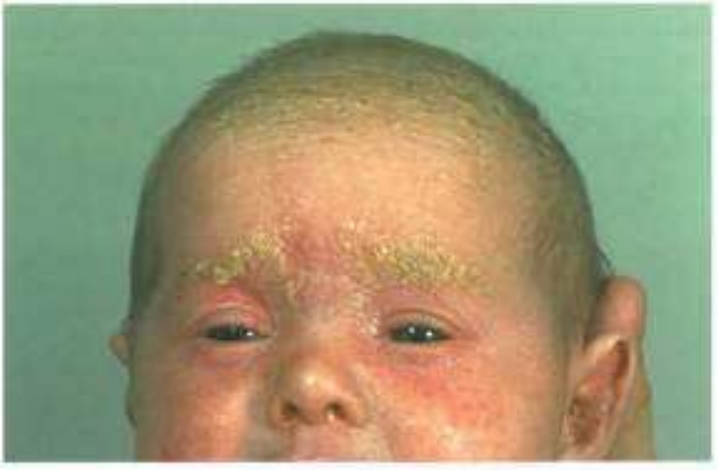


Fig. 3.43 Seborrhoeic eczema. It may subsequently spread from the scalp to the face, particularly the eyebrows, cheeks and ears. 1% hydrocortisone ointment is the treatment of choice.

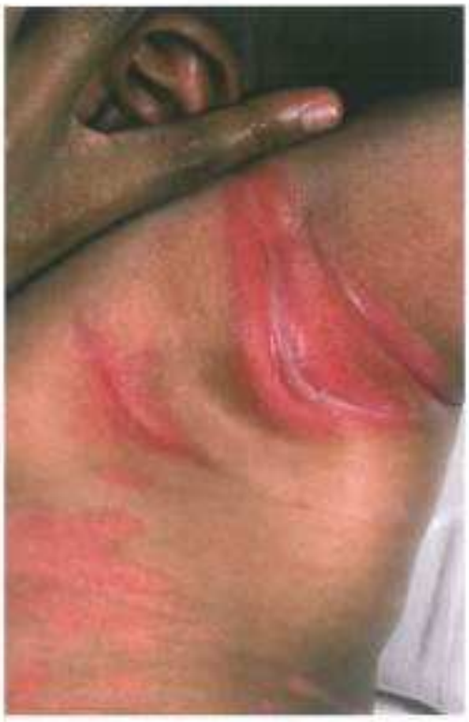


Fig. 3.44 Seborrhoeic eczema.
The intertriginous areas (axillae and groin) are involved in seborrhoeic eczema as opposed to flexures in atopic eczema.

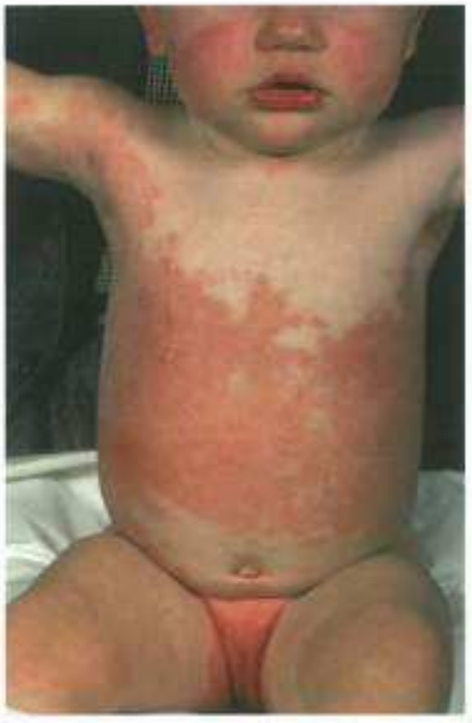


Fig. 3.45 Seborrhoeic eczema. It may become extensive, involving the trunk, axillae and groin. It causes little distress to the infant.

Differential Diagnosis

The main differential diagnosis of infantile seborrhoeic eczema is infantile atopic dermatitis (Fig. 3.46). Erythrodermic seborrhoeic dermatitis does occur and rarely may be confused with:

- **Leiner's syndrome** A triad of an erythrodermic seborrhoeic dermatitis (Fig. 3.47) associated with failure to thrive and diarrhoea has been described and is known as *Leiner's syndrome*. For a long time it was thought that this could be caused by biotin-deficient breast milk. Subsequently, Miller reported defective serum opsonization of yeast by normal neutrophils in an infant with the features of Leiner's syndrome who was also prone to a variety of infections. It was thought to be a functional abnormality of C5, but this defect occurs quite commonly in the community and C5-deficient serum can sustain normal opsonization. The current status of the syndrome is therefore unclear. Nonetheless, it is wise to check an unwell infant with erythrodermic eczema with a susceptibility to infection for immunodeficiency.
- **Omenn's syndrome** This is an erythroderma, with severe combined immunodeficiency, eosinophilia and significant lymphadenopathy due to a disorder of RAG 1 and 2 genes.
- **Maple syrup urine disease** Exfoliative erythroderma resulting from inadequate intake of branched chain amino acids has been described in infants with this disorder.

Management

- **Reassurance** The condition improves over the ensuing few weeks even if the eruption is quite florid.
- **Treatment of the cradle cap** Arachis oil is useful. Salicylic acid (2%) in aqueous cream is helpful for removing the crusts. Higher concentrations should be avoided, since this theoretically could lead to salicylism.
- **Emollients**
- **Topical steroids** The condition does respond to mild topical steroids. Hydrocortisone (1%) ointment is the drug most commonly used, but occasionally moderately potent steroids are required. Some dermatologists advocate combining the steroid with an antibacterial and an anticandidal agent, but this is not essential.
- **Pityrosporicidal drugs** There are no clinical studies of the pityrosporicidal theory but these drugs may prove effective, particularly in combination with hydrocortisone.
- **Secondary infection** Bacterial sepsis may occur but infection with *Candida albicans* is probably overdiagnosed.

Napkin dermatitis

A primary irritant contact dermatitis caused by prolonged exposure to body fluids occurring in the napkin area.

Aetiology

It is not known why some babies develop it and others do not. It is not usually caused by inexperience, for frequently the mother has brought up other babies without this problem. It is less common in breast-fed babies and more common in those who have diarrhoea and are treated with antibiotics. The most vulnerable are those who attend creches and daycare centres, where gastroenteritis is common. Napkin dermatitis is considered to be caused by constant and prolonged immersion of the skin in urine and faeces, compounded by impervious plastic pants surrounding the sodden napkin. Friction from the napkin and pants, and the maceration which results from the wet body fluids, abrade and disrupt the protective barrier of the skin. It has been demonstrated that urine which has been allowed to stand for several hours at body temperature will induce a dermatitis when applied to the skin, whereas fresh urine will not, which would suggest that prolonged periods without a napkin change are an important factor. Probably, faecal lipases and proteases hydrolyse urinary urea, releasing ammonia, which in turn acts as an irritant. *C. albicans* is often isolated from napkin dermatitis but is regarded as a secondary invader of macerated skin.

Clinical Features

Symptoms

It begins during the first few months of life and the infant may not be particularly bothered by the condition.

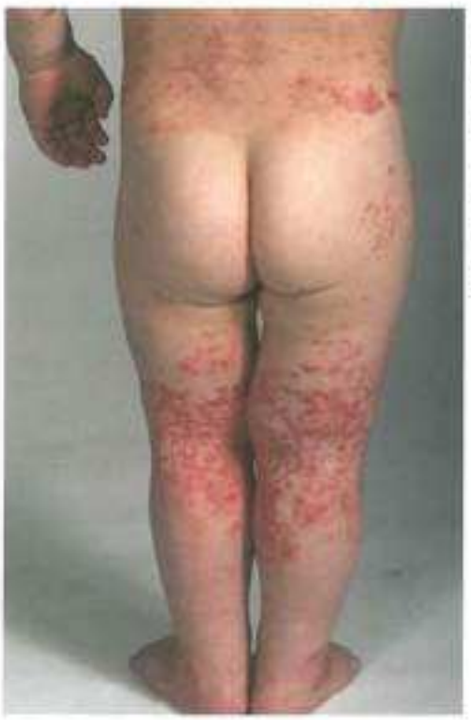


Fig. 3.46 Atopic eczema. Atopic eczema begins at 3 months. Seborrhoeic eczema begins at about 6 months. The distribution is different. Atopic eczema favours the limb flexures and seborrhoeic eczema the axillae and napkin area. Both involve the face.

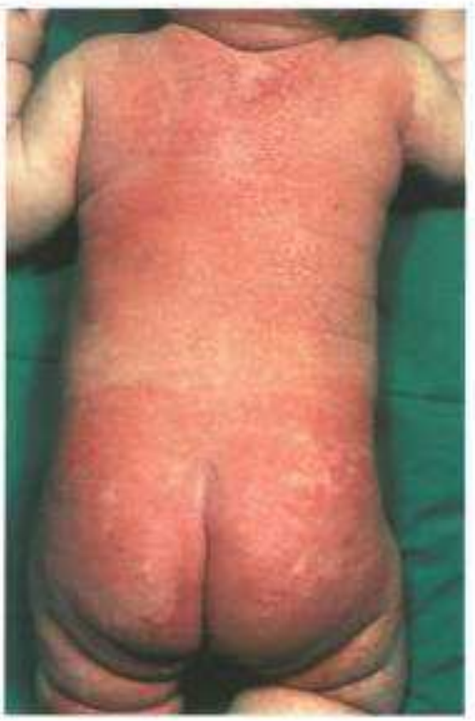


Fig. 3.47 Erythrodermic seborrhoeic dermatitis. If seborrhoeic eczema is associated with failure to thrive and diarrhoea, a diagnosis of immunodeficiency or Leiner's syndrome should be considered, but the latter, if it exists, is very rare.

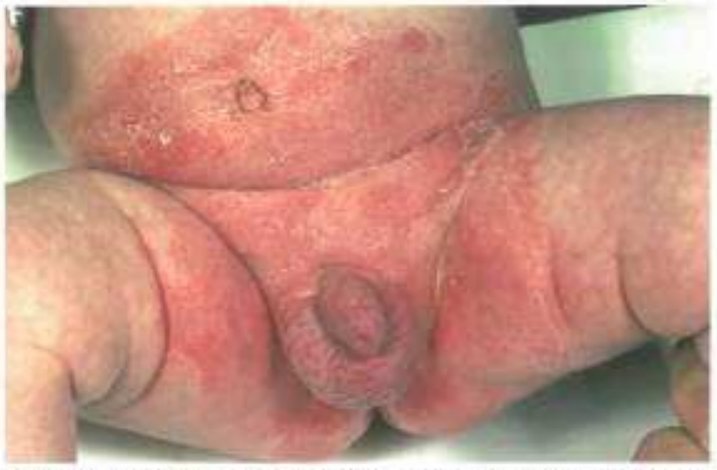


Fig. 3.48 Napkin dermatitis. This results from prolonged contact of the skin of susceptible babies to urine and faeces in a soiled napkin.

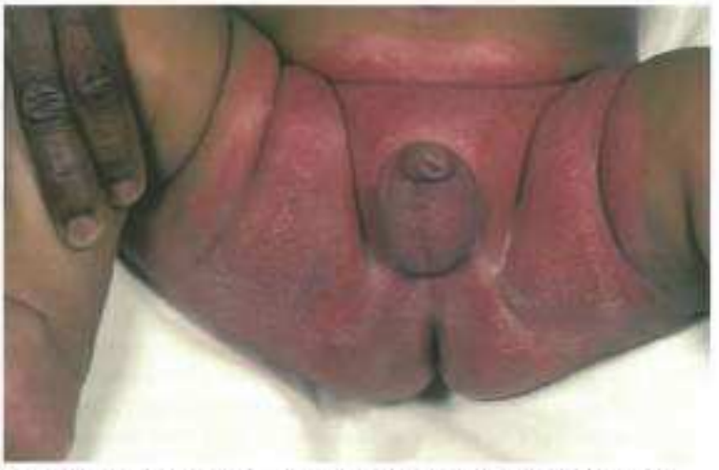


Fig. 3.49 Napkin dermatitis. The eruption conforms to the convex surfaces covered by the napkin. There is confluent erythema with scaling.

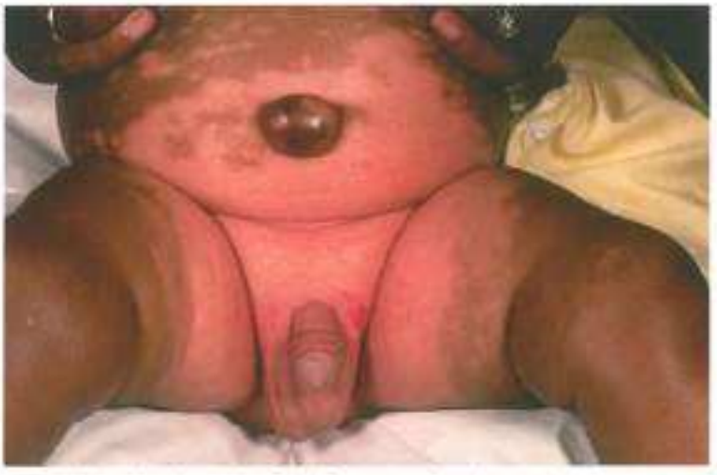


Fig. 3.50 Napkin dermatitis. Postinflammatory hypopigmentation is a common consequence of eczema in dark skins, including after napkin dermatitis.

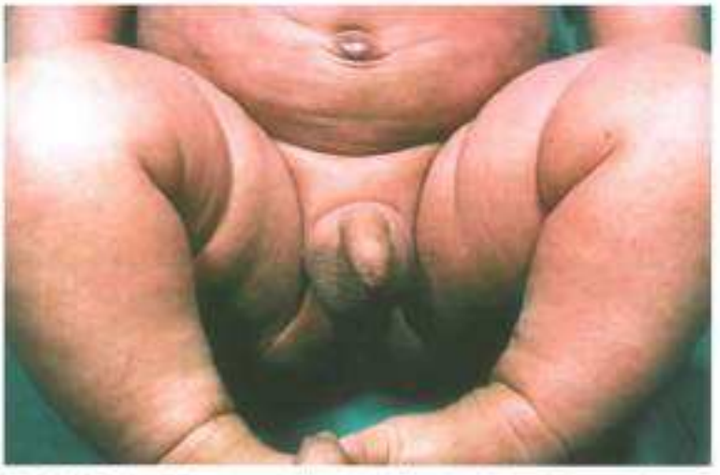


Fig. 3.51 Seborrhoeic eczema. It may be difficult to distinguish from a primary irritant napkin dermatitis but it is usually accompanied by signs elsewhere such as cradle cap.

Morphology

There is a confluent erythema with some scaling on the convex surfaces covered by the napkin (Figs 3.48 and 3.49). Postinflammatory hypopigmentation (Fig. 3.50) is common in dark skins and this takes several months to repigment. A variant of seborrhoeic eczema (Fig. 3.51) is *Jacquet's napkin dermatitis* (Fig. 3.52) (a more traumatic insult to the skin, often a result of inexperience or neglect, from the soiled and sodden napkin being left in contact with the skin for many hours) which results in blisters and erosions (Fig. 3.53).

Distribution

The eruption involves the convex surfaces covered by the napkin (lower abdomen, pubic area, buttocks, genitalia and upper thighs). The genitocrural flexures are spared.

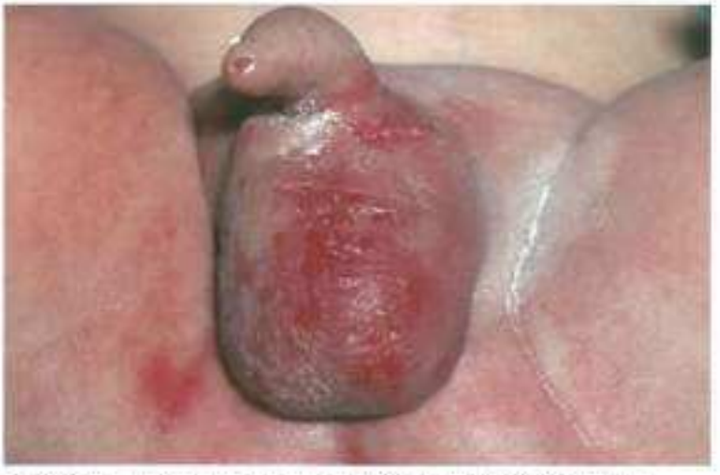


Fig. 3.52 Jacquet's napkin dermatitis. Erosions are clearly seen on the scrotum. This results from failure to change the napkin regularly, through inexperience or neglect.

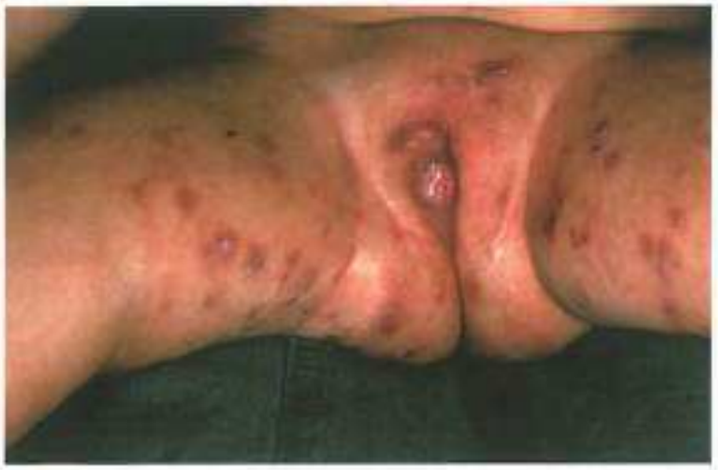


Fig. 3.53 Jacquet's napkin dermatitis. This papulo-erosive eruption is not common but is caused by a soiled and sodden napkin being left for too long in contact with the skin.

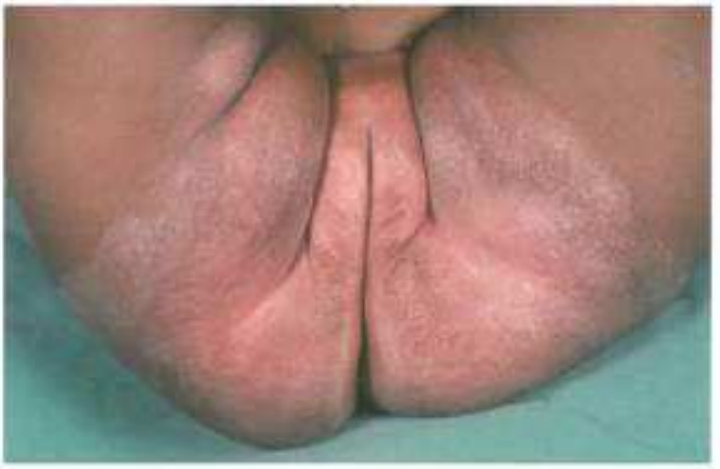


Fig. 3.54 Napkin psoriasis. This is red and well demarcated, particularly in the napkin area, and is probably a manifestation of the Koebner phenomenon in an infant with a psoriatic disposition.

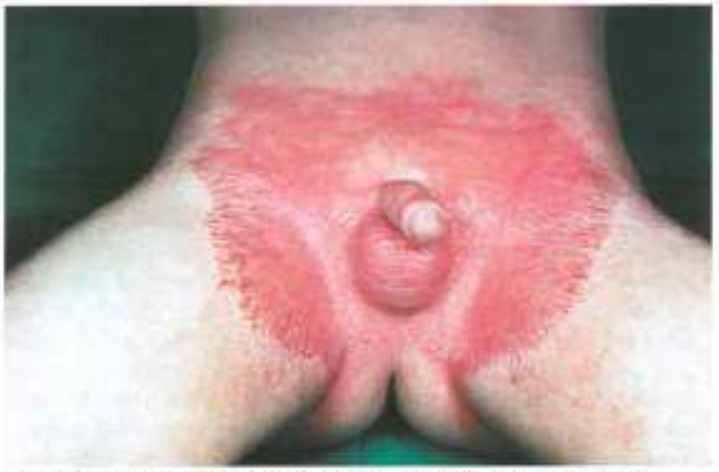


Fig. 3.55 Napkin psoriasis. Psoriasis is a very defined condition with well demarcated edges. The deep red colour and pronounced scale distinguish it from eczema.

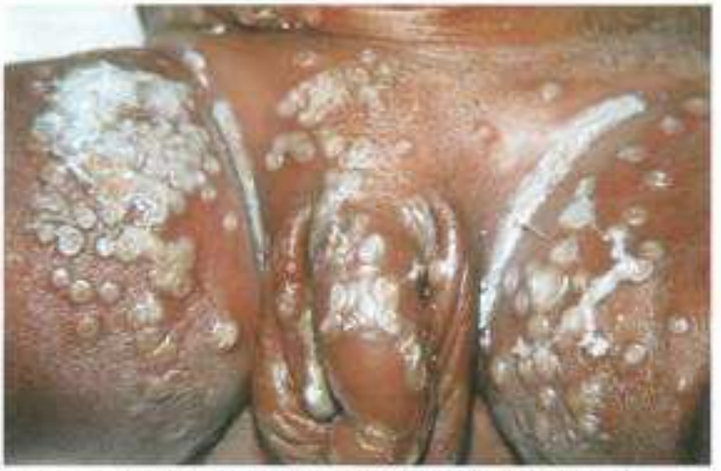


Fig. 3.56 Kaposi's varicelliform eruption. There are striking umbilicated vesicles. This is usually seen in an atopic. In this case, herpes simplex was isolated and treated with aciclovir.

Differential Diagnosis

- **Candidiasis** This is not particularly common but there is a rawness and maceration of the genitocrural folds with satellite pustules. The latter suggests the diagnosis and a swab for culture will confirm it.
- **Napkin psoriasis** There are dry, red, well-defined plaques (Figs 3.54 and 3.55) with a white silvery scale in the napkin area and often elsewhere.
- **Herpes simplex infection** This may occur as a primary infection but more often as a manifestation of eczema herpeticum (Fig. 3.56). There are well-defined vesicles to be found and the infant may be quite unwell. The diagnosis can be established by Tzank smears or PCR.
- **Acrodermatitis enteropathica** The infant is miserable, has diarrhoea and fails to thrive, secondary to malabsorption of zinc (Ch. 22). There are vesiculo-bullous lesions that crust and erode around orifices, particularly on the face, anus and genitalia. The diagnosis can easily be missed. Zinc levels are low and the response to zinc replacement is dramatic.
- **Langerhans' cell histiocytosis** There are discrete red papules with a purpuric component (Fig. 3.57). A biopsy will prove the diagnosis.

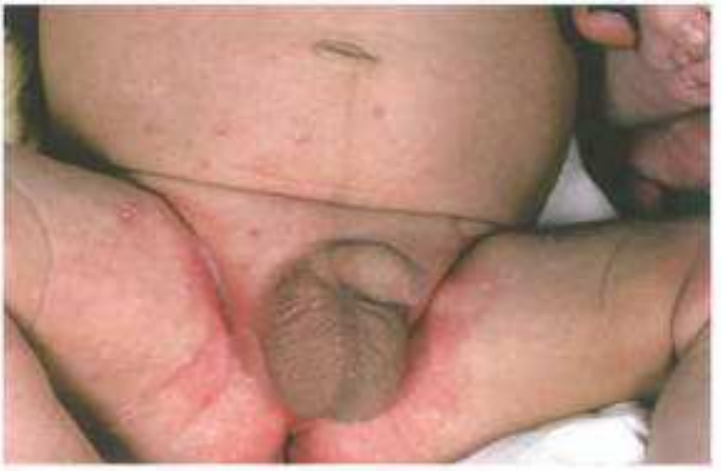


Fig. 3.57 Langerhans' cell histiocytosis. There are discrete purple papules. This was misdiagnosed by a paediatrician as a napkin eruption but the papules are striking and a biopsy proved the correct diagnosis.

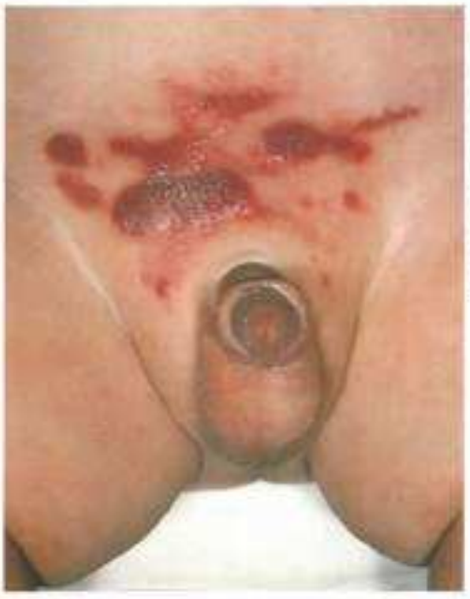


Fig. 3.58 Infantile gluteal granuloma. Purple nodules are present in the napkin area. The cause is unknown but it may be related to the use of occlusive plastic pants and, possibly, potent topical steroids. It gradually resolves spontaneously.

- **Infantile gluteal granuloma** There are several livid oval, purple nodules, which presents quite a striking appearance on the convexity of the napkin area (Fig. 3.58). The disorder is assumed to be caused by changes in care of the napkin area (in particular the use of plastic occlusive pants) and to treatment with potent topical steroids. Although the child may have or have had a napkin dermatitis there is no correlation with severity. The real cause is *sub judice* but removal of these factors does lead to improvement. Equally, cases remit spontaneously even if potent steroids are continued. Histologically there is a dense granulomatous infiltrate occupying the whole of the dermis.

Adult seborrhoeic dermatitis

An eczematous process of varying degrees of severity, with a propensity for the scalp and face and sometimes the flexures and upper trunk, associated with overgrowth of the yeast *Pityrosporum* (*Malassezia*) *ovale*.

Aetiology

The cause is unknown, but the fungus *Pityrosporum* (*Malassezia*) *ovale* is found among the scales of seborrhoeic dermatitis and may be cultured from them. Experimental infection with the organism does reproduce the disease, but *P. ovale* may also be found in unaffected skin and agents effective against *P. ovale* do not cure the condition. The yeast may represent an epiphenomenon, because the disorder responds to topical steroids, which theoretically should make an infection worse. The prevalence in the population is 5%, but is much greater with HIV positivity and especially AIDS, possibly immunosuppression permits secondary infection with this commensal and hence causes seborrhoeic dermatitis.

The term 'seborrhoeic' is a misnomer. The dry, yellow scales of the disease were thought to represent dried sebum, but in fact they are exfoliated cells of the stratum corneum. Although the eruption occurs on the face and the front and back of the chest, where there are a large number of sebaceous glands, it is also encountered in sites where there are few sebaceous glands (e.g. the groins and axillae).

The disorder is common in adults, particularly of Celtic ancestry, and has been noted in association with Parkinson's disease. In its minor form, it is frequently associated with stress and anxiety. Many patients note that it disappears temporarily on a relaxing holiday, particularly in the sun. The more widespread disease is less common in the West than it was, possibly caused by improved standards of nutrition and health.

Clinical Features

Symptoms

The main symptoms are flaking, redness and dryness of the skin.

Morphology

There is a variable degree of ill-defined roughness, redness and scaling of the skin (Fig. 3.59). The patches may be annular (Fig. 3.60).

Distribution

Although considered part of the same disease, it is possible to recognize three entities based on the distribution of the eruption.

- **Face and scalp** This is the commonest form and in most individuals does not progress to the other types. It occurs on the glabella, eyelids (marginal blepharitis), ala of the nose (Fig. 3.61), eyebrows, moustache area, sideburns and ears. One or all of these sites may be involved. The condition is symmetrical and often does not itch at all, unlike other forms of eczema. The scalp is most commonly involved, as either a dandruff (an exaggeration of the normal process of exfoliation of the cells of the stratum corneum) or coupled with an ill-defined erythema, when it is classified as a true seborrhoeic eczema.
- **Presternum and upper back** The condition is chronic and consists of fairly well-defined pink, scaly, annular patches over the sternum (Fig. 3.62), and the interscapular area.

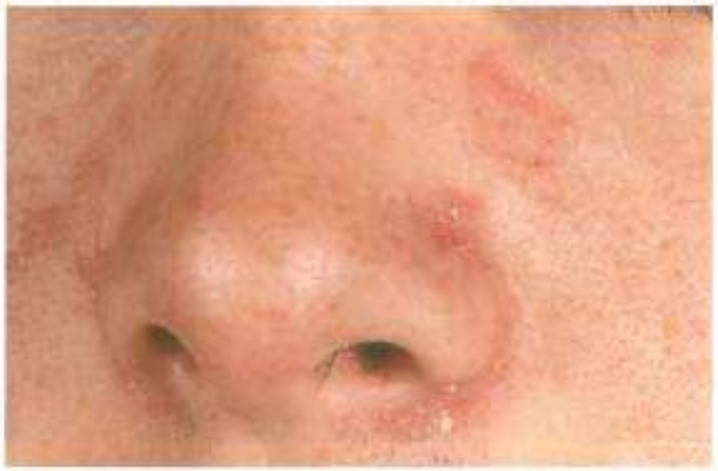


Fig. 3.59 Adult seborrhoeic eczema. The sides of the nose are dry, pink and scaly. The eyebrows, ears, cheeks and scalp are also often involved.

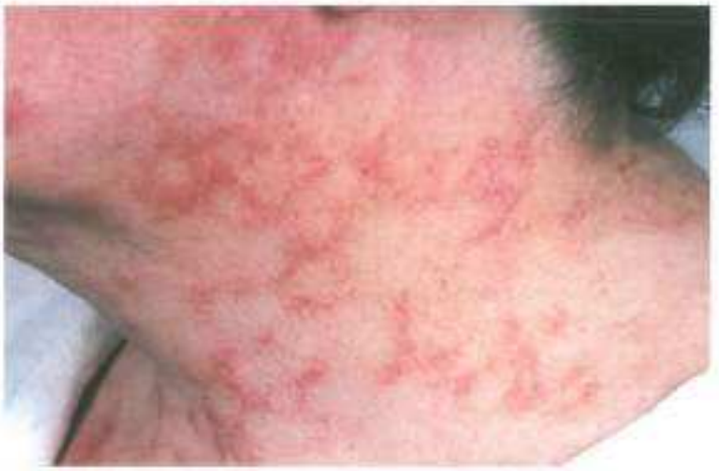


Fig. 3.60 Seborrhoeic eczema. The lesions may be strikingly annular in shape but at the same time red and scaling.

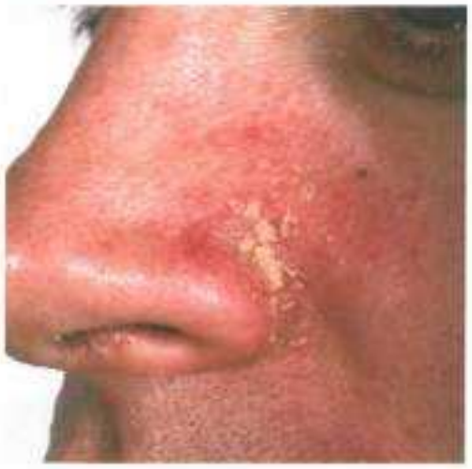


Fig. 3.61 Adult seborrhoeic eczema. Ill-defined scaly patches occur around the nose. The more prominent cases are less easy to treat and sometimes turn out to be psoriasis.

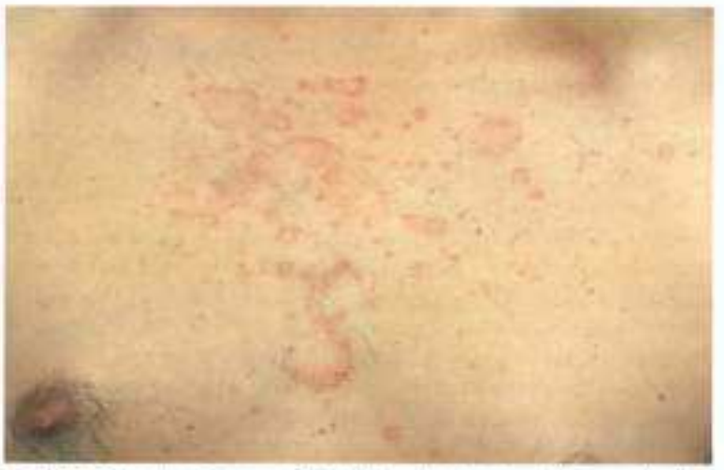


Fig. 3.62 Seborrhoeic eczema. The skin is red and scaly and often annular. It may be remarkably persistent on the presternal and interscapular areas.

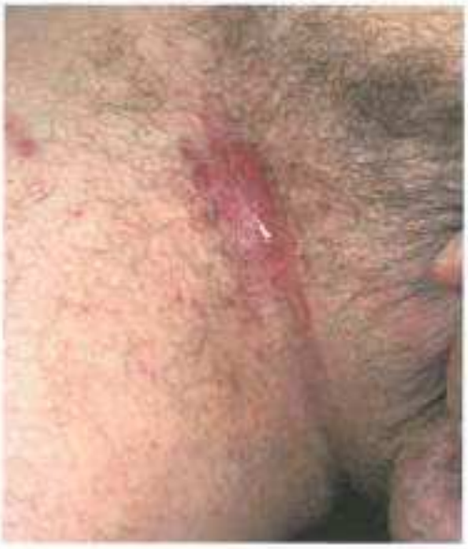


Fig. 3.63 Seborrhoeic eczema. Although infections are common in the groin, there is no advancing raised margin and the inguinal fold is involved (unusual for tinea). Mycology was negative. This is seborrhoeic eczema in a patient misusing alcohol.

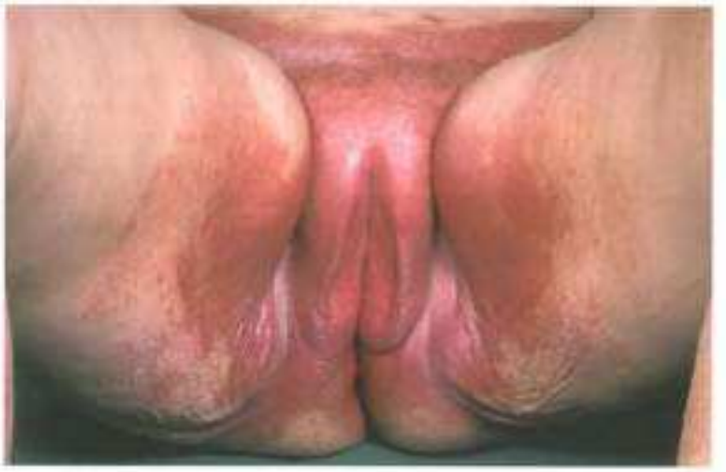


Fig. 3.64 Intertriginous seborrhoeic eczema. There is a symmetrical erythema and some redness around the vulva. The eruption may be severe but responds to topical steroids.

- **Flexural seborrhoeic eczema** This form of intertrigo involves the major flexures in the obese and middle aged. It is symmetrical and either pink with a fine scale or bright red, raw and sore (Figs 3.63 and 3.64).

Differential Diagnosis

Scalp

- **Psoriasis** (Fig. 5.45)
- **Pityriasis amiantacea** (Fig. 26.37)

Face

- **Acne** (Fig. 24.25)
- **Sebopsoriasis** (Fig. 3.65)
  This is a variant of psoriasis occurring in the distribution of seborrheic dermatitis which is more difficult to treat and this in itself may suggest the diagnosis. The lesions of psoriasis are a deeper red colour than the pink of seborrhoeic eczema and the scales are thicker.

Presternum and upper back

- **Pityriasis versicolor** (Fig. 6.22)
- **Pityrosporum folliculitis** (Fig. 15.23)
- **Darier's disease** (Fig. 20.44)

Intertrigo

- **Tinea** (Fig. 15.56)
- **Candidiasis** (Fig. 15.9)
- **Erythrasma** (Fig. 13.29)

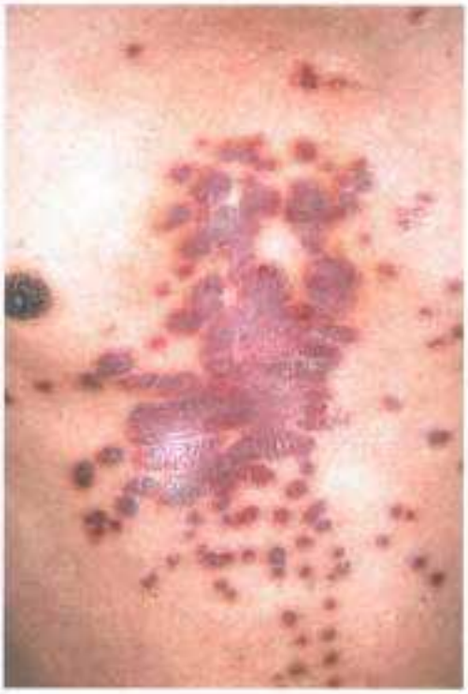


Fig. 3.65 Sebopsoriasis. The presternum is a classic site for seborrhoeic dermatitis but these lesions are too red and well demarcated for eczema and are due to psoriasis.

Management

Many patients are undergoing a high degree of pressure either at work or in their personal lives. Alcohol misuse is common.

Scalp

Tar, imidazoles and topical steroids are the mainstays of treatment. Calcineurin inhibitors are proving to be promising.

Minor seborrhoeic eczema of the scalp is commonly called dandruff. It responds well to frequent washing (often daily) with tar, selenium sulphide or imidazole shampoos. Ketoconazole (Nizoral) shampoo is effective against *P. ovale* and is a major advance in the management of dandruff. If eczema is present, potent topical steroids are required, particularly since the thickness of the scalp prevents adequate penetration of weaker steroids. In more severe seborrhoeic dermatitis and particularly pityriasis amiantacea, cocois (a combination of tar, salicylic acid and coconut oil) is more effective.

Face

Usually 1% hydrocortisone is effective. Although ointments are preferable, it is reasonable to use creams because they are more cosmetically acceptable. The patient should be warned not to put the steroid in the eye. Potent steroids are not indicated as they cause a perioral or periorbital acne. Imidazoles are often prescribed for their activity against *P. ovale* but are probably more effective if used in combination with 1% hydrocortisone. Lithium succinate (5%) applied topically can be useful although its mechanism of action is not understood. It may cause an irritation of the skin and for that reason it may be used with hydrocortisone. Protopic 0.1% (Tacrolimus) is effective.

Other measures

Oral itraconazole Itraconazole is being used more frequently, at a dose of 100 mg daily for up to 3 weeks; sometimes gratifying long-term remissions are obtained.

Antibiotics Some patients do have a minor degree of concomitant acne vulgaris and hydrocortisone may exacerbate it; for this reason, systemic low-dose antibiotics for a few months may be necessary. Full doses are required for infected major forms of seborrhoeic eczema.

Presternum and upper back

Topical steroids

It does not respond to hydrocortisone but does to potent steroids, although it tends to relapse quickly.

Antibiotics

Patients often have acne in addition to adult seborrhoeic dermatitis and may require long-term oral antibiotics.

Oral imidazoles

Oral imidazoles are worth trying, particularly if the patient has a concomitant seborrhoeic (pityrosporial) folliculitis.

Phototherapy

Adult seborrhoeic dermatitis does respond to ultraviolet B therapy although it subsequently tends to relapse.

Seborrhoeic intertrigo

Minor variants

Weak topical steroids are effective because flexural areas are warm and moist, allowing efficient penetration of the drug. Because there is sometimes secondary infection with bacteria and *Candida* sp., combined preparations may be used, e.g. miconazole, which has antibacterial and anticandidal activity, and 1% hydrocortisone.

Major variants

The major variant of seborrhoeic intertrigo may be quite inflamed and widespread and often requires rest and occasionally hospitalization. The principles of therapy are:

- **Soaks** Saline, aluminium acetate or potassium permanganate soaks are most commonly used, in a bidet, bowl or bath. Potassium permanganate does stain the nails and the patient should be warned to wear rubber gloves. Soaks for 10 minutes once or twice daily are sufficient, after which the area should be patted dry with a paper towel or an old dispensable towel.
- **Topical steroids** Moderately potent topical steroids are usually required and often need to be coupled with an antibiotic and antifungal agent (e.g. clobetasone butyrate, oxytetracycline and nystatin).
- **Systemic antibiotics** Erythromycin or flucloxacillin are the antibiotics of choice, as with other forms of infected eczema.

Discoid (nummular) eczema

Discoid eczema is a morphological description of an eczema that constitutes a distinct disorder in older individuals but may be an extension of atopic eczema in youth. It particularly affects the limbs.

Aetiology

In young adults, it is thought to be part of an atopic diathesis where the rash occurs on the limbs rather than in the flexures. It occurs in white and black skins. In the elderly, the cause is unknown. It particularly affects the professional classes, is more common in males and IgE levels are generally normal. Some patients misuse alcohol and the condition is often worse in winter. Secondary infection with staphylococci is common in both types and it may have an aetiological role. Occasionally, discoid eczema is mimicked by a reaction to methyldopa and certainly diuretics may exacerbate the disease in the elderly. The histology is of a subacute eczema.

Clinical Features

Symptoms

Discoid eczema is particularly itchy.

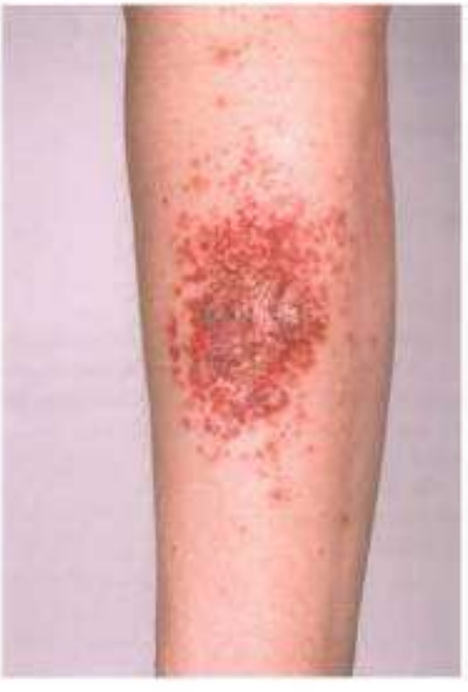


Fig. 3.68 Discoid eczema. The patches are relatively well defined, round, pink and scaly. They are very itchy. It requires potent or superpotent topical steroids.

Morphology

The lesions are well defined and round, hence the term 'nummular' (Latin *nummus*: coin) (Figs 3.66 and 3.67). The surface is dry, rough, red and covered with a fine scale. If secondary sepsis has occurred, there is weeping and crusting (Fig. 3.68). In young sun worshippers, it may cause temporary hypopigmentation (Fig. 3.69).

Distribution

The limbs (Fig. 3.70), including the backs of the hands, are particularly affected but the condition may occur on the trunk. It is quite characteristic that old scars may be involved.

Differential Diagnosis

- **Tinea** These lesions are round but they are distributed asymmetrically and the margin is most active with a tendency to central healing.
- **Psoriasis** The lesions are discoid but the scale is much thicker and the lesions are a deeper red than the pink of eczema.
- **Chronic superficial scaly dermatosis** These lesions may be circular or finger-like in shape but they are to be found on the inner rather than the outer aspects of the limbs and they have a rather wrinkled atrophic surface. The lesions do not respond to topical steroids.

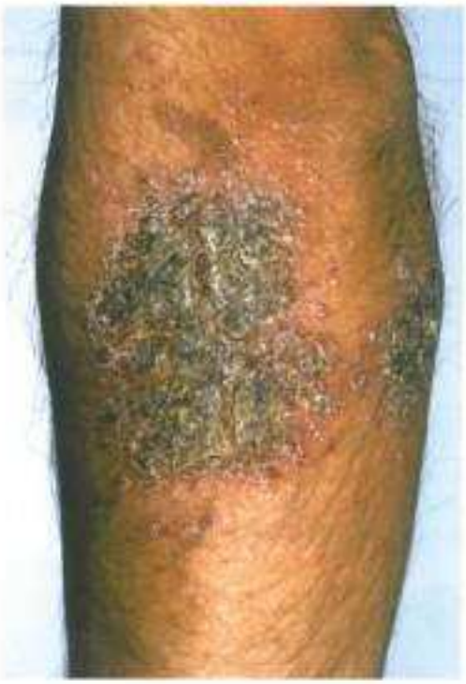


Fig. 3.67 Discoid eczema. In young adults discoid eczema is part of atopy. It occurs in all races. Secondary sepsis as in this patient with yellow crusts secondary to oozing purulent material is common.

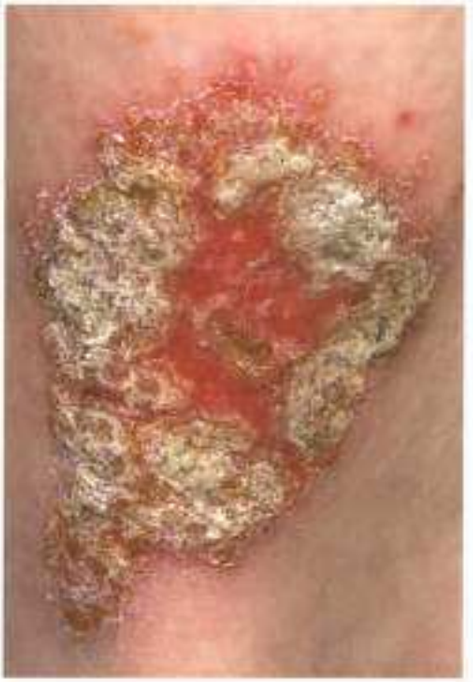


Fig. 3.68 Discoid eczema (septic). The patches frequently are subacute or acute and weep and become purulent with yellow crusts.

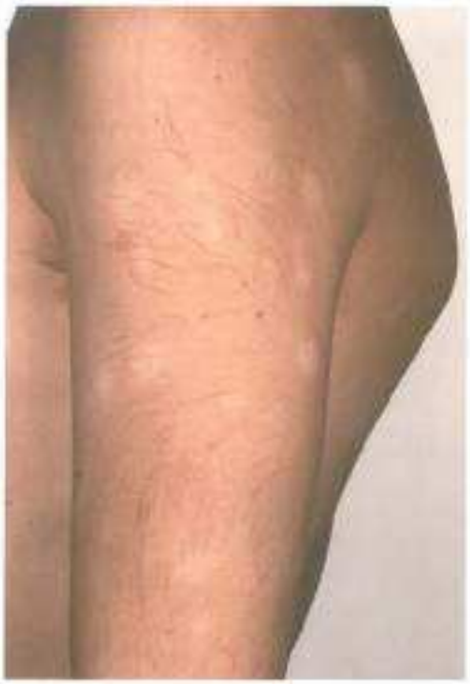


Fig. 3.69 Discoid eczema (hypopigmented). In young adult sunlovers, the discoid eczema often results in hypopigmented patches on the limbs, which are mistaken for pityriasis versicolor.

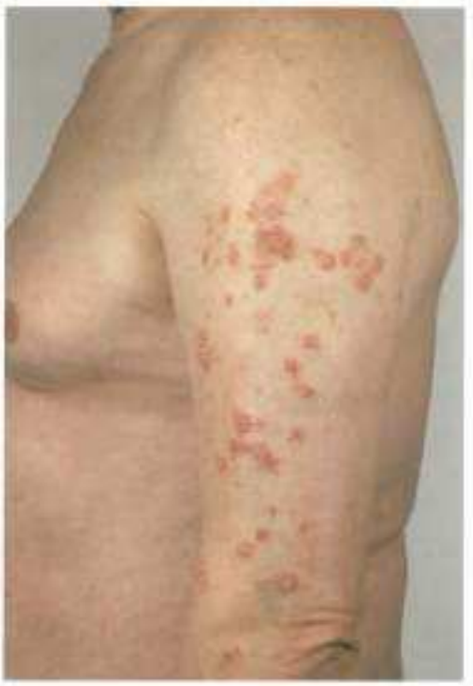


Fig. 3.70 Discoid eczema. Itchy, coin-shaped (nummular) lesions occur on the limbs. There may be a systemic cause in elderly patients afflicted with it. A full blood count and biochemical analysis is indicated.

Management

Potent or superpotent steroids are necessary. Secondary sepsis is common and combination with an antibiotic or systemic antibiotics may be necessary. Emollients and antihistamines are useful adjuncts. A full blood count and biochemical analysis may be illuminating (Fig. 3.71). Myelodysplastic syndrome may present with discoid eczema and overindulgence in alcohol is a feature in the elderly.

The hypopigmented variety is not easy to manage. Advice not to sunbathe, thus allowing the normal skin to return to its previous pale colour and to blend in with the hypopigmented area, is usually not greeted with any enthusiasm. The eczematous patches should be treated with steroids, but the hypopigmented patches recover slowly and may take many months. This disorder does go into remission after a few years.

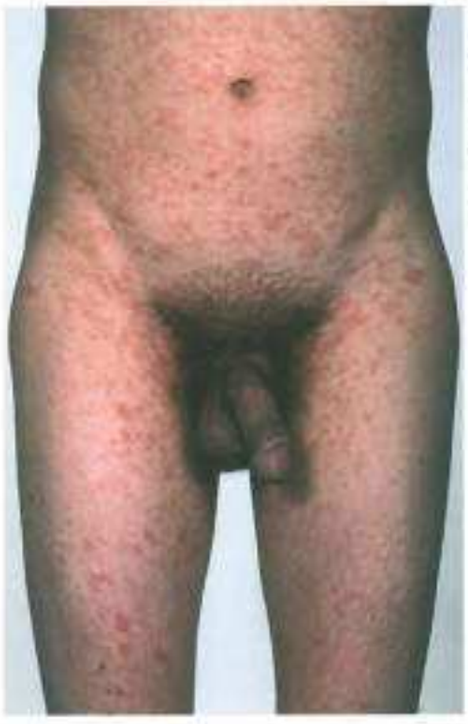


Fig. 3.71 Discoid eczema. The lesions are extensive. The patient's consumption of alcohol was considerable. Failure to elicit a history of alcohol misuse (either binge drinking or regular excess) is a common error.

Pompholyx (dyshidrotic eczema)

A distinctive pruritic vesicular eruption of the palms and soles and sides of the digits associated with hyperhidrosis; it may become dry, fissured and chronic.

Aetiology

The cause of this common condition is unknown. Pompholyx affects both sexes, is most frequent in youth and early middle age and is usually precipitated by warm weather. Many patients sweat easily on the palms and soles, hence its alternative name, dyshidrotic eczema. Although this hyperhidrosis must be relevant, the theory that the bubbles represent beads of sweat no longer receives any scientific support. Some patients have an annual attack lasting 3 or 4 weeks every summer. Others have a chronic course. Some have an atopic background. A few are positive to perfumes, medicaments or topical steroids on patch testing, and avoidance of the allergen may solve the problem. Quite a few are positive to nickel but avoidance of this both in terms of contact and in the diet has variable results and the relevance of this finding is not understood.

Occasionally, a satisfactory explanation is forthcoming when the pompholyx on the hands represents a reaction to a cutaneous problem on the feet, either an acute tinea or contact dermatitis. However, this is often overdiagnosed because pompholyx is not restricted to the hands (*cheiropompholyx*) but frequently occurs on the feet (*podopompholyx*). Many of the patients are under intense pressure and it is one of the skin disorders where psychological factors are deemed particularly relevant.

Clinical Features

Symptoms

The patient complains of intensely itchy small 'bubbles' under the skin of the palms and sides of the fingers, which subsequently break, weep and dry out (Fig. 3.72) rendering the skin cracked and painful (Fig. 3.73).

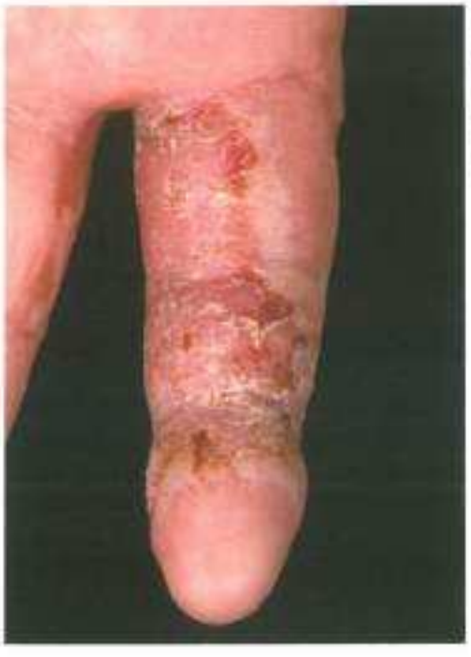


Fig. 3.72 Pompholyx. The vesicles break, weep and may become impetiginized. Patch tests are usually negative. Potent topical steroids are helpful.

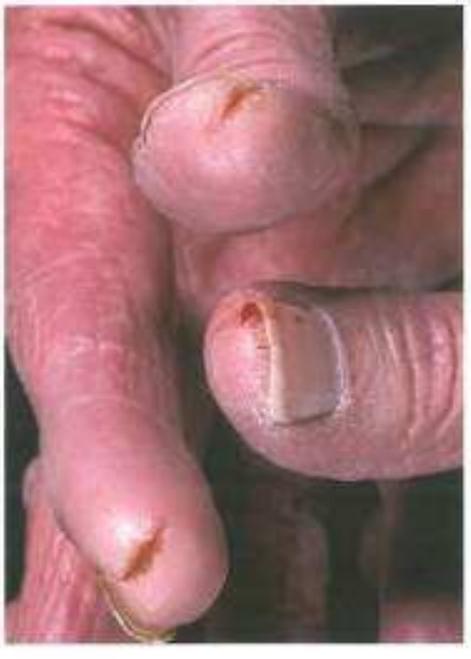


Fig. 3.73 Pompholyx. The vesicles subsequently dry and the skin may become fissured and painful. These changes may be chronic.

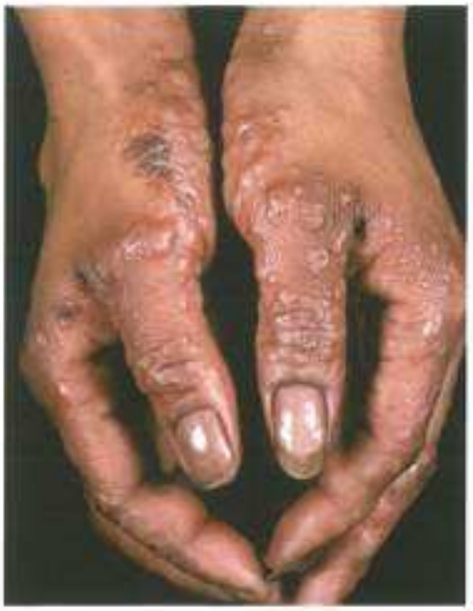


Fig. 3.75 Pompholyx. Many blisters are present. The patients frequently suffer from hyperhidrosis and are atopic. Stress and alcohol misuse are relevant precipitants.

Morphology

The eruption is remarkably symmetrical (Figs 3.74 and 3.75). Tiny vesicles are present (Fig. 3.76), which may coalesce, resulting in massive incapacitating blisters (Fig. 3.3). Secondary infection is common in the more acute cases (Fig. 3.77) leading to a lymphangiitis and lymphadenopathy. Eczema herpeticum (Fig. 3.78) occasionally occurs.

Distribution

The palms and soles and the sides of fingers and toes.

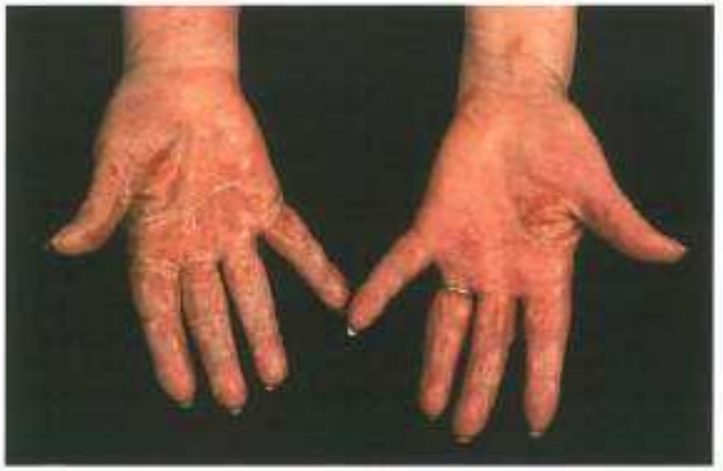


Fig. 3.74 Pompholyx. Palmar eczema is often vesicular (pompholyx) and endogenous. There may be a personal or family history of atopy. Patch tests however are worthwhile to rule out a contact allergen.

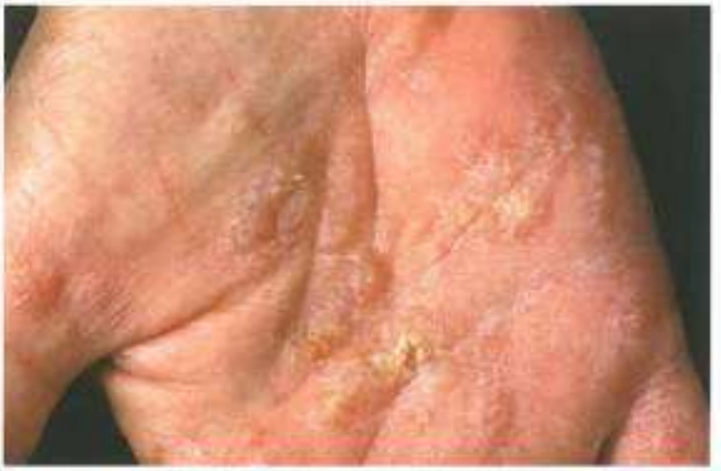


Fig. 3.76 Pompholyx. Intensely itchy vesicles, which may become confluent, occur on the palms and sides of the fingers, particularly in the summer.

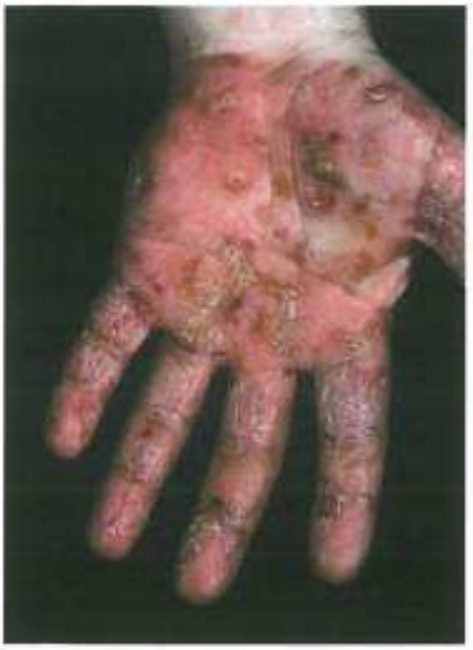


Fig. 3.77 Pompholyx. The vesicles may coalesce and the eruption may become extensive. Secondary bacterial sepsis may ensue. Systemic steroids, antibiotics, topical steroids and saline soaks are indicated.

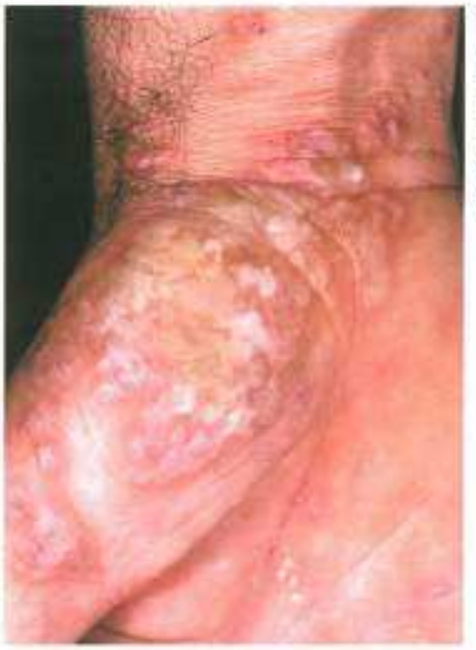


Fig. 3.78 Eczema herpeticum. Herpes simplex may occur on the hand in patients with a predisposition to pompholyx. Discrete vesicles have become confluent on the hypothenar eminence.

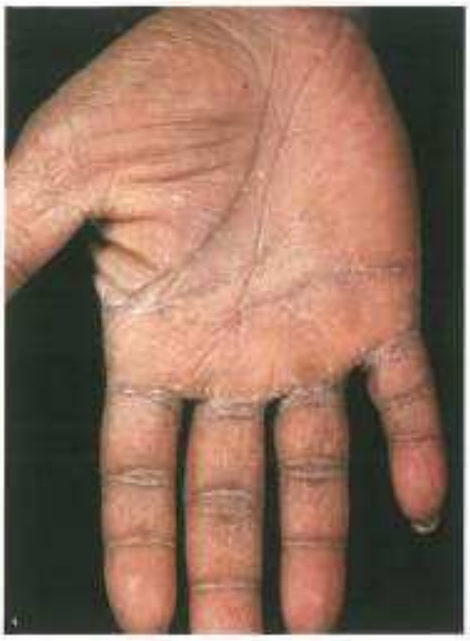


Fig. 3.79 Tinea. The skin is dry and there are crescentic scales and a powdery involvement of the skin creases. The obvious clue to the diagnosis, however, is that usually one hand only is involved.

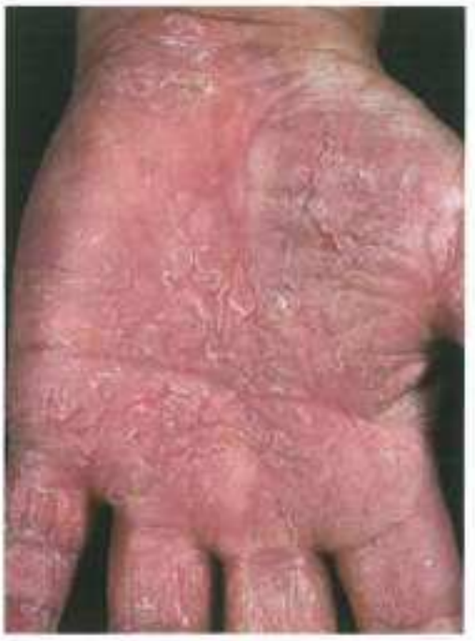


Fig. 3.80 Psoriasis. When psoriasis affects the hands alone, diagnosis is not easy. The skin, scalp and nails should be examined for confirmatory diagnostic proof. The lesions are well defined, pink and fissured. It is resistant to topical therapy. Methotrexate or acitretin may be indicated.

Differential Diagnosis

- **Tinea** Only one palm is involved. There is a powdery scaling in the skin creases (Fig. 3.79) and the nails may be affected. It may be acute and vesicular on the feet and invariably this is unilateral. Chronic tinea does affect both feet and toenails but asymmetrically with crescentic scales and fine white scaling in the plantar creases.
- **Contact dermatitis** One can never be certain that one has ruled out contact dermatitis until patch tests have been done.
- **Psoriasis** In psoriasis, there are no vesicles, the scale is much thicker and the plaques are relatively well defined (Fig. 3.80). Splitting of the skin is common. Pustules are apparent in pustular psoriasis.
- **Lichen planus** (Fig. 3.81).
- **Keratolysis exfoliativa** This is a common short-lived recurrent minor variant of pompholyx (syn. recurrent focal peeling), where small areas of focal desquamation occur on the palms (Figs 3.82 and 3.83). It rarely gives rise to any symptoms, although anxious patients sometimes request an explanation. There is no specific treatment.

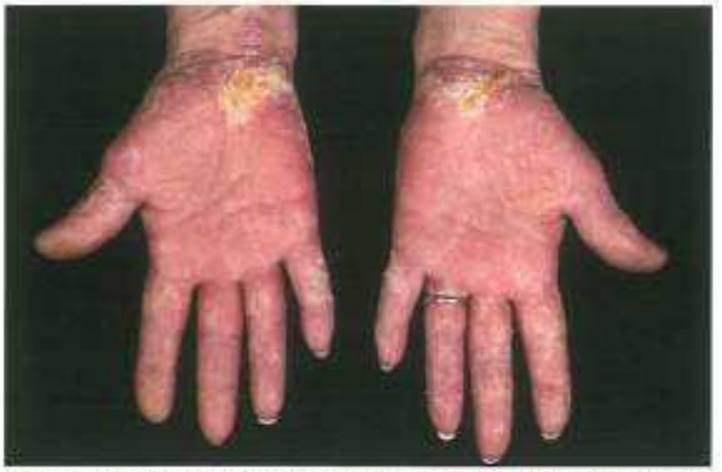


Fig. 3.81 Lichen planus. On the back of the hands, the purple, shiny, flat-topped papules are easily diagnosed. On the palms, the lesions may be yellow and hyperkeratotic although the purple may be visible at the periphery.

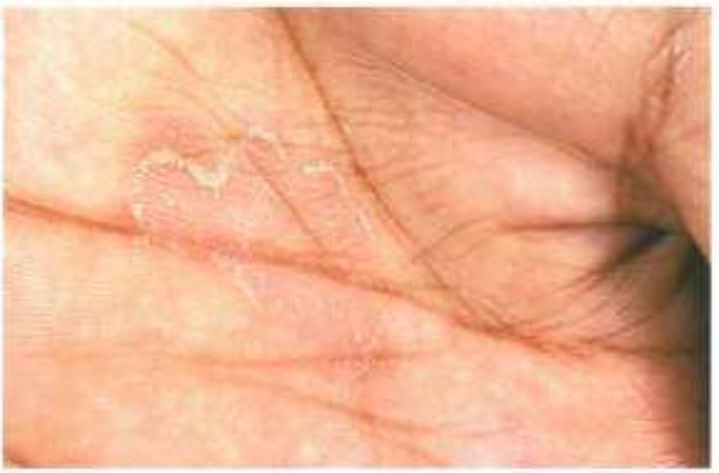


Fig. 3.82 Keratolysis exfoliativa. A fine exfoliation (peeling) occurs on the palms and fingers in hot weather. It is a minor variant of pompholyx.

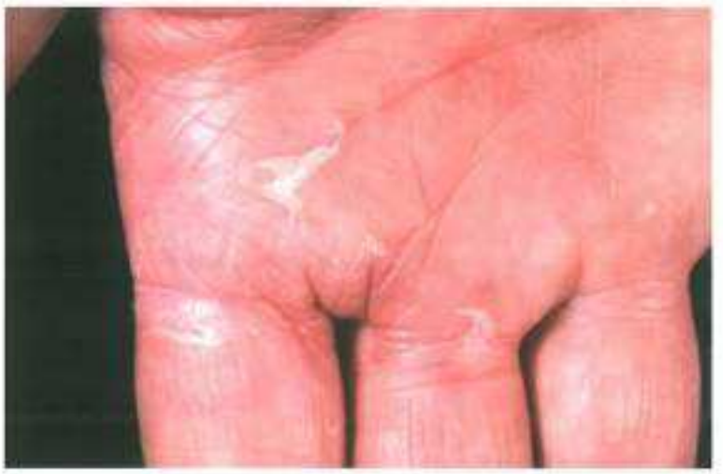


Fig. 3.83 Keratolysis exfoliativa. Periodic focal acral peeling is common. Continuous acral peeling from an early age is rare, may be inherited and in some cases a transglutaminase 5 mutation has been demonstrated.

Management

Acute vesiculo-bullous pompholyx

An acute pompholyx of the hands is occasionally secondary to an acute fungal infection on the feet. Scrapings should be taken from the skin of the feet for mycological examination. Inappropriate treatment of a pompholyx on the feet with an antifungal agent may so irritate the skin as to initiate an autosensitization eczema on the hands. Many patients suffering from pompholyx have stressful lives and appropriate treatment may be helpful.

Acute attacks settle with soaking the skin in saline. Burrow's solution (5% aluminium acetate) or (and especially for the feet) potassium permanganate for 5–10 minutes once or twice daily followed by applications of potent topical steroids. However, systemic steroids are the treatment of choice if there are no medical contraindications. Prednisolone (30 mg) is prescribed and the dose is reduced by 5 mg every fourth day. They lead to improvement within 48 hours. Since secondary sepsis is usually present, systemic antibiotics are required.

Subacute and chronic pompholyx

Potent or superpotent steroids are indicated as they do dry up the vesicles and relieve the irritation. Weaker steroids are ineffective because they do not penetrate the thick palmar skin adequately. The steroids should not be spread onto the non-affected skin on the dorsal aspects of the hands, otherwise unnecessary atrophy will occur. A combination with antibiotics is indicated if pustules or yellow crusts (sepsis) are present. Systemic steroids are sometimes necessary in chronic disease but should be avoided as much as possible. Emollients are useful for the second stage when dryness and fissuring predominate. Oral antihistamines are useful sedatives and antipruritics.

Juvenile plantar dermatosis

A symmetrical eruption of the weight-bearing plantar surfaces of the feet in children, probably secondary to occlusive synthetic footwear.

Aetiology

The condition seems to be a relatively recent phenomenon and is thought to be a consequence of the change in the composition of socks and shoes. Natural materials such as cotton, wool and leather are steadily being replaced by synthetic materials such as nylon and plastics, which are less porous. The loss of permeability is enhanced by the various repellent coatings that are applied to shoes in order to improve their durability. A contact dermatitis to some part of the footwear has been suspected, but patch testing has been unproductive.

The condition affects children and young adolescents, particularly those who continually wear the 'trainer' type of footwear. Some of the patients are atopic, but this is not by any means a consistent finding. They are often keen on football and other sports and it may be that the hot and humid environment produced by these occlusive shoes, coupled with the friction to which the active child subjects the skin, sets up the disorder.

Clinical Features

Symptoms

Juvenile plantar dermatosis can be asymptomatic or involve soreness.

Morphology

The skin has a red, glazed and cracked appearance and the eruption is quite symmetrical (Figs 3.84 and 3.85).

Distribution

The plantar surfaces of the weight-bearing areas of the foot (toes, forefoot and lateral sides of the feet) are affected. The toe clefts and the instep are spared.

Differential Diagnosis

- **Tinea** Although the condition is frequently misdiagnosed as athlete's foot, the symmetry, the sparing of the toe webs and the negative mycology will differentiate the two.

Management

The management of juvenile plantar dermatosis is difficult as many children refuse to change their footwear and even if they do, this does not necessarily produce a cure. Nonetheless, they should be advised to adopt leather shoes and cotton socks and to change their shoes regularly throughout the day, returning to the old-fashioned principle of indoor and outdoor shoes. Periods of time free of footwear are advocated. Many of the children seem little troubled by the condition and it gradually disappears over a number of years as they enter adolescence.

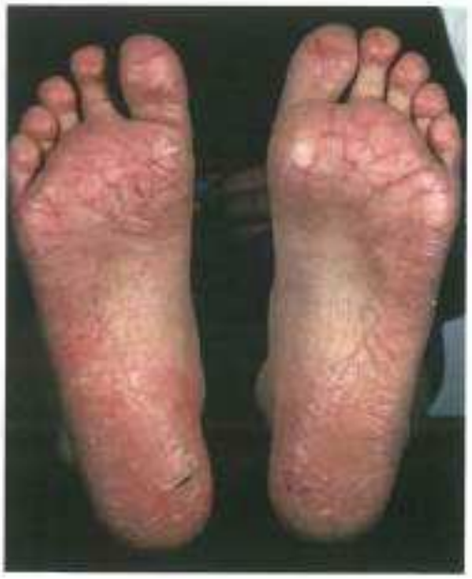


Fig. 3.84 Juvenile plantar dermatosis. The condition may be related to the occlusive effect of modern "trainer" footwear. It ultimately resolves.

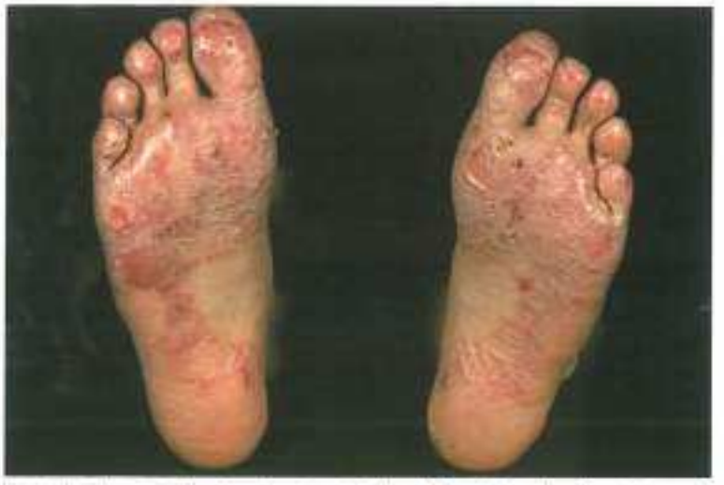


Fig. 3.85 Juvenile plantar dermatosis. This childhood disorder affects the weight-bearing areas of the soles, is symmetrical, well defined, red glazed and fissured.

Topical steroids

These steroids do not seem to be of any great help, whatever potency is tried; although they may have some initial benefit this soon wears off.

Emollients

Emollients are the treatment of choice.

Lichen simplex

Lichen simplex is an eczematous response to continual rubbing and scratching of a localized area of the skin.

Aetiology

This is a dermatological example of a 'habit tic', often initiated by a stressful life event. Continual rubbing and scratching results in thickening of the skin with exaggeration of the skin creases, a phenomenon known as *lichenification*. Lichen simplex can be induced in anyone, provided the stimulus to the skin is continued for long enough. Histologically, there is acanthosis and hyperkeratosis. The rete ridges are lengthened and spongiosis is sometimes present. The dermis contains a chronic inflammatory cell infiltrate.

Clinical Features

Symptoms

The condition is intensely itchy.

Morphology

There may be one or several well-defined patches of thickened skin, with marked accentuation of the skin creases (Fig. 3.86). Postinflammatory hyper- or hypopigmentation is common in darker skins.

Distribution

These patches are often unilateral, corresponding to the handedness of the patient, and are in those areas that the patient can easily scratch and rub, such as the nape of the neck, eyelid, just below the elbow, hand, inner aspect of the thigh, outer aspect of the lower leg, buttock, ankle and genitalia (Figs 3.87 and 3.88).

Differential Diagnosis

The diagnosis is not difficult but any itchy condition may become lichenified through continued scratching and rubbing, most obviously atopic eczema but occasionally tinea and psoriasis.

Management

Topical corticosteroids

The condition responds to superpotent corticosteroids. Potent steroids may also be effective but usually have to be applied under polythene occlusion or injected as triamcinolone intralesionally. The only exception to the use of these strong steroids is when lichen simplex occurs on the face, where it responds to 2.5% hydrocortisone ointment.

Fig. 3.86 Lichen simplex. There is a solitary well-defined thickened plaque with marked accentuation of the skin creases, which are visible in a criss-cross pattern.

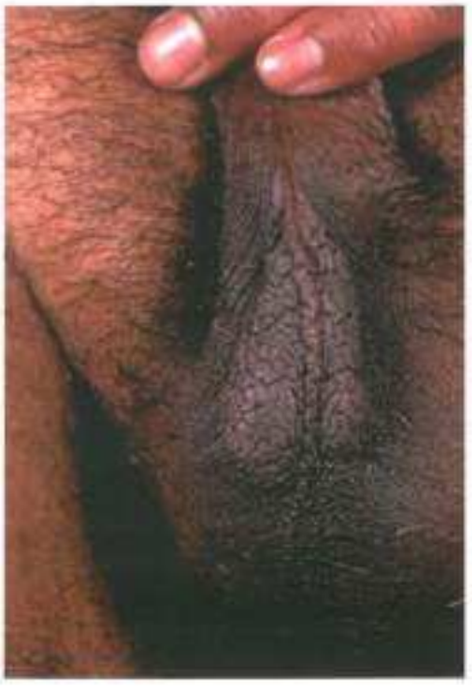


Fig. 3.87 Lichen simplex. The exaggeration of the skin creases and thickening of the skin is very obvious. The disorder is usually very itchy and secondary to rubbing of the skin; it is often precipitated by stress.

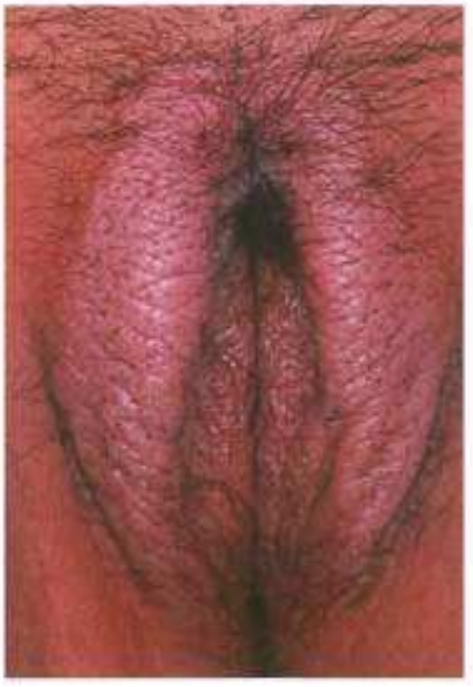


Fig. 3.88 Lichen simplex. The genitalia are often involved. The skin markings are clearly delineated. The condition is often, but not always, unilateral. It responds to potent steroid ointments.

Systemic antihistamines

Sedative antihistamines, e.g. hydroxyzine hydrochloride starting at 10 mg and increasing by 20 to 30 mg, are often required to prevent the patient from scratching, particularly at night, while the steroid acts on the eczema. It is very important to point out to the patient not to scratch during treatment, because this only aggravates the disease.

Identification of precipitating factors

The condition usually commences during a period of stress. Enquiries should be made regarding this, although the stress will often have passed. The condition persists because the eczema, once developed, will only respond to anti-eczema therapy. In some patients, chronic neurosis is present and the condition having been treated then reappears elsewhere. In this case it is known as *lichen simplex chronicus*, for it is remarkably persistent over many years (Fig. 3.89).

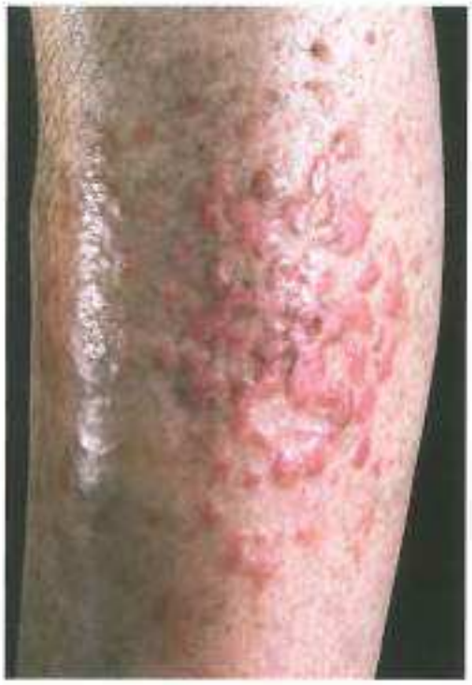


Fig. 3.89 Lichen simplex chronicus. Sometimes the habit of interfering with the skin is difficult to break and the condition becomes chronic, often on the leg. Superpotent steroids and occlusive bandages may be helpful.

Lichen striatus

Lichen striatus is a self-limiting linear form of eczema that occurs in children or young adults.

Aetiology

The pathology of the condition is that of eczema, but the cause is quite obscure. Most cases occur in children between the ages of 5 and 15 years. Females are most commonly affected. There may be classical eczema at other sites, or a family history of atopy suggesting an immunological cause. It has been proposed that an infective agent or trauma mediates an autoimmune CD 8^+ inflammatory response directed against a mutated keratinocyte clone. This is somatic and post fertilization which would explain the linear arrangement of the eruption along Blaschko's lines.

Clinical Features

Symptoms

Lichen striatus is mildly pruritic.

Morphology

There are lichenoid papules that result in postinflammatory hypopigmentation (Figs 3.90 and 3.91).

Distribution

The condition arises in a linear or zosteriform distribution either along a limb or across part of the trunk. The nail may be involved.

Management

The condition is distinctive. A linear epidermal naevus may cause confusion but is present at birth and it persists, whereas lichen striatus resolves within 2 years. There is no specific treatment, though class III topical steroids may alleviate the itch.

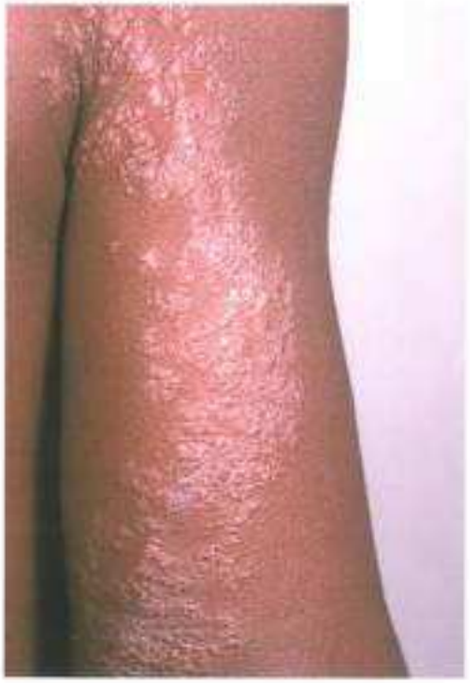


Fig. 3.90 Lichen striatus. This is a self-limiting linear form of eczema characterized by lichenoid papules and postinflammatory hypopigmentation.

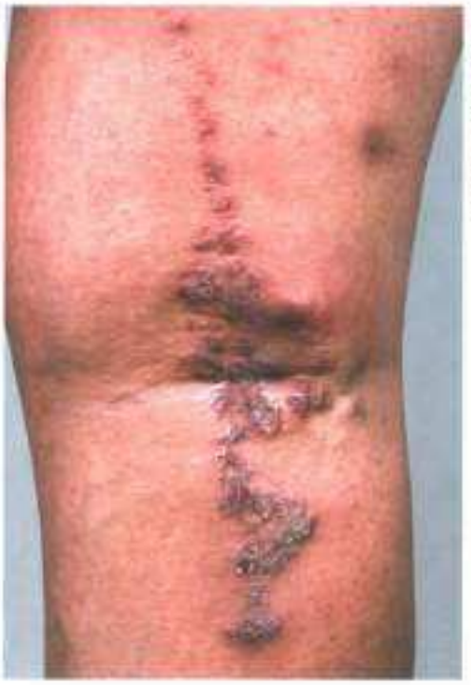


Fig. 3.91 Lichen striatus. The linear arrangement of lichenoid papules along one limb is distinctive. The cause is unkown but the pathology is eczematous. It may respond to potent topical steroids.

Contact dermatitis 4

Contact dermatitis is an eczematous reaction resulting from the interaction of an external substance with the skin. These reactions are either irritant or allergic in origin. The former can affect anyone provided that the irritant agent is sufficiently concentrated and the exposure is prolonged enough. The latter only occurs in the predisposed, is a delayed hypersensitivity allergic reaction and will recur every time the allergen is encountered.

Primary irritant dermatitis is not the result of an immunological reaction but of cumulative damage to the outer protective layer of the skin, the stratum corneum. Certain individuals are more prone to it, particularly atopics. Strong irritants such as caustics will clearly produce such a reaction, but this is not within the framework of this discussion. The reaction may occur anywhere on the skin. In children, incontinence (napkin dermatitis) (Fig. 4.1) (see Ch. 3), lip licking (see Fig. 3.24), dribbling and thumb sucking may all result in a primary irritant form of dermatitis. In adults, cumulative damage may result in *primary irritant dermatitis* of the hands. In the elderly, a condition on the shins known as *asteatotic eczema* (*eczema craquelé*) can occur, which merits separate description here.

Allergic contact dermatitis is a true allergic type IV hypersensitivity (Gel and Coomb's classification). The allergen is usually a low-molecular-weight chemical that links with a protein, thus becoming a hapten. It is processed by Langerhans' cells and macrophages and then transported via the lymphatics to the paracortical area of the lymph nodes. Here the thymus-derived lymphocytes are primed and then returned to the skin via lymphatics or blood vessels, where they will be ready to react with the antigen. This priming takes approximately 7–10 days. On subsequent exposure to the antigen, this cell-mediated reaction results in a dermatitis within 48 to 72 hours.

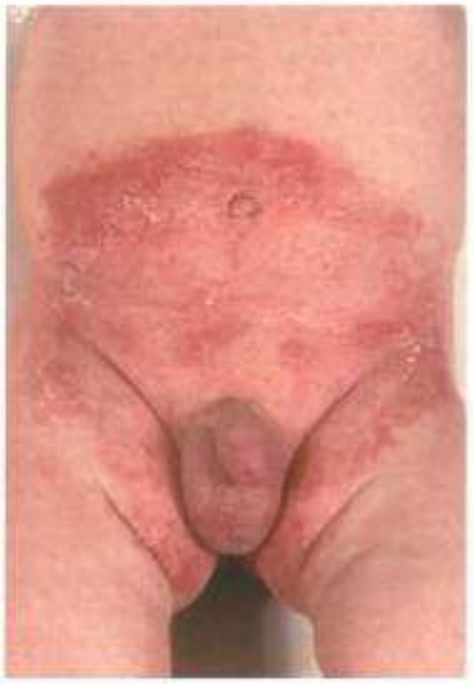


Fig. 4.1 Napkin dermatitis. The eczema is largely confined to the area covered by the diaper and results from cumulative insults to the skin from incontinence. It is an example of a primary irritant dermatitis

Photocontact dermatitis is an interaction between a photosensitizing chemical and ultraviolet light that produces either a toxic or an allergic response. Phototoxic reactions are non-immunological, so anyone can develop the reaction given sufficient exposure to the chemical and ultraviolet light. The reaction may be either local or systemic. The latter is considered under drug and light eruptions. The common local reactions are *phytophotodermatitis* and *Berloque dermatitis*.

Primary irritant dermatitis of the hands

An eczematous eruption, mainly on the backs of the fingers and hands, occurring in those whose occupations require frequent immersion of the hands in water and exposure to irritants.

Aetiology

The disorder is common, primarily affecting young adult females, who are often atopics. Although colloquially known as 'housewife's dermatitis', it occurs in any occupation in which there is constant exposure to water and irritants such as detergents and shampoos. Hairdressers, nurses, chefs, cleaners and mechanics are amongst the vulnerable. It is estimated that 50% of junior hairdressers develop some degree of primary irritant dermatitis of the hands during their apprenticeship (which largely consists of shampooing). Many are nickel-sensitive subjects; the relevance of which is unexplained: one study found that the exclusion of nickel-sensitive subjects from the profession greatly reduced the incidence of hand eczema.

Clinical Features

Symptoms

The skin is itchy and sometimes sore.

Morphology

Ill-defined, pink, rough, scaly and sometimes fissured patches (Fig. 4.2).

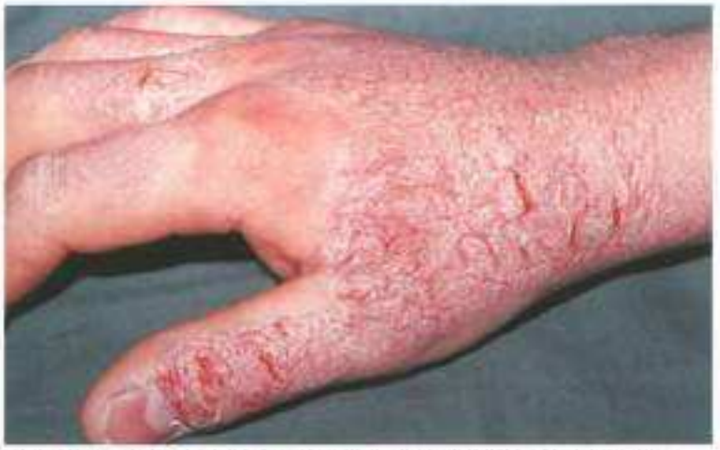


Fig. 4.2 Primary irritant dermatitis. The skin is dry, pink, scaly and fissured. The backs of the hands are particularly affected. This young man was an atopic, working as a mechanic.

Distribution

The eczema usually begins under a ring, probably because of the concentration of soap or detergent that becomes trapped under a ring, but the friction of the ring is important in causing mild trauma to the skin. The ring is usually transferred to another finger and the eczema begins there and then gradually spreads to the backs of the fingers and hands (Fig. 4.3) but there is a characteristic sparing of the palms. If the skin around the posterior nailfold is involved, nail growth may be disturbed, resulting in horizontal linear ridges across the nail plate.

Management

The skin must be kept out of water as much as possible. It is useful to get the patient to write out a list of the previous day's activities and to discuss how much water exposure was really necessary. If possible clothes should be washed by machine, not by hand.

Patch tests are valuable because what may appear to be an irritant dermatitis may turn out to be allergic.

Potent topical glucocorticosteroids are necessary. Hydrocortisone is ineffective. It is important, however, to instruct the patient to apply the ointment to the lesions only, and not to spread it generally all over the backs of the hands, to prevent unnecessary side-effects (Fig. 4.4). Emollients should be used liberally and are important substitutes for soap. Coal tar solution may be added to it. The eczema is pruritic, and sedative antihistamines are sometimes required.

Sometimes, a primary irritant dermatitis of the hands reflects an inability of a wife and mother to cope with her situation, such that she neglects herself and allows the skin to deteriorate. In a sense, therefore, it is a cry for help. She sees herself as servicing her partner, the house and the children and getting little attention in return. The condition rapidly responds to hospitalization, where the patient is given attention and looked after. The condition tends to be a prolonged one in some patients and it is often because these factors are not rectified that the condition continues.

It may be necessary to change occupation. For example, a change from the operating theatre to outpatient duties may be all that is required for a nurse. For hairdressers, the condition may improve when they become senior and no longer have to wash the customers' hair. As a matter of policy, it is always sensible to advise atopics against entering a profession that requires this type of exposure.

Asteatotic eczema (eczema craquelé)

A dry, superficially fissured skin disorder, often on the shins of the elderly, precipitated by the drying effect of a cold winter or excess washing.

Aetiology

This is a disorder of the elderly. There is possibly a reduction in skin surface lipids and the condition is occasionally a presenting feature of myxoedema. The patients may have had a tendency to slight dryness of their skin all their lives, or the dryness may have developed as they have aged, especially if they are sun damaged. The histology is that of an eczema. It is a form of primary irritant dermatitis and is usually precipitated by (i) a cold winter with low relative humidity; (ii) admission to hospital and more frequent bathing of the skin than the patient is used to; (iii) installation of central heating without adequate humidification, leading to a dry atmosphere; and (iv) diuretics.

Clinical Features

Symptoms

The skin is sore and itchy.

Signs

The appearance is characteristic, with many superficial fissures criss-crossing over the skin surface (Fig. 4.5). The skin is red, dry and scaly.

Distribution

The shins are the most characteristic site of involvement (Fig. 4.6).

Management

The prognosis is usually good if the skin is properly cared for. Emollients are crucial and the time spent explaining lubrication is well rewarded. To emphasize the point, the nurse or doctor should apply an emollient to the skin at the consultation. Potent topical steroids in an ointment and not a cream form (otherwise the dryness will be exacerbated) are helpful. Bathing should be restricted to twice a week and emulsifying ointment used instead of soap. There should be no wool next to the skin.

Allergic contact dermatitis

This is a delayed hypersensitivity reaction that results in dermatitis. Once an individual has become sensitized, the potential to react persists and the dermatitis will recur if the patient is re-exposed to the allergen.

Aetiology

The most frequently encountered antigens outside of industry are metal, rubber, perfumes, nail varnish, some plants (e.g. poison ivy, primula), dyes, cosmetics (e.g. preservatives, lanolin), colophony (adhesive dressings), epoxy resins (glues) and acrylates and phenol formaldehyde resins (present in glues, paints and wood preservatives).

The most common industrial agents are chromates in cement, resins in the plastic industry, dyes, rubber and glues.

Industrial dermatitis tends to remit at the weekend or during a holiday, i.e. when the patient is not at work. Other workers may be similarly affected. Since this diagnosis may lead to litigation and unemployment, expert advice is required, often from a dermatologist specializing in industrial medicine.

There are many contact allergens, and referral for patch tests is necessary. Direct questioning about present and past occupations and hobbies is essential. It is wise to ask the patient to bring to the patch test clinic everything in their medicine cabinet or on their dressing table that might at any time have been put onto the skin,. If the allergen is not identified promptly and the patient continues to be exposed, a chronic dermatitis may result despite removal of the antigen at a later date. New sources of allergens (e.g. sofas treated with fungicides imported from China) are regularly encountered.

Clinical Features

Symptoms

The patient often gives a history of intense irritation, blisters and weeping of the skin.

Morphology

Allergic contact dermatitis is an eczema (often acute or subacute).

Distribution

The clue to the diagnosis is the distribution of the eruption. For example, the backs of the hands and around the wrists might suggest rubber gloves; the feet, shoes; the neck in a female, perfumes; and the waist, metal studs in jeans. The lack of any past history of eczema as a child and the failure to control the eruption adequately with topical steroids might also indicate that an allergen is responsible. Often the face (Figs 4.7 and 4.8) is involved.

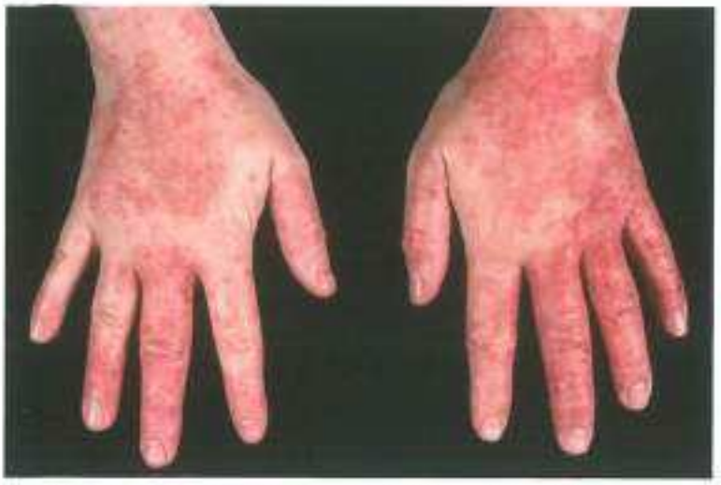


Fig. 4.3 Primary irritant dermatitis. Ill-defined, dry, pink, fissured patches occur on the backs of the fingers and hands. Patch testing is necessary to exclude a contact allergen.

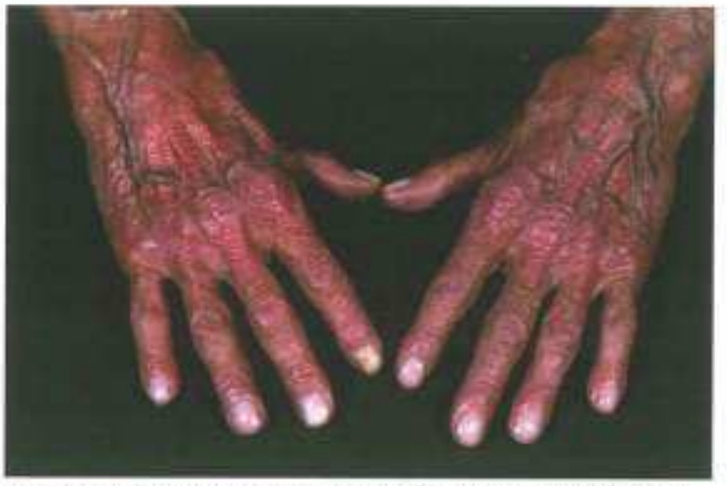


Fig. 4.4 Misuse of topical steroids. Topical steroids penetrate the skin of the back of the hands easily and prolonged use of potent steroids will cause atrophy of the skin. The vasculature is clearly visible.

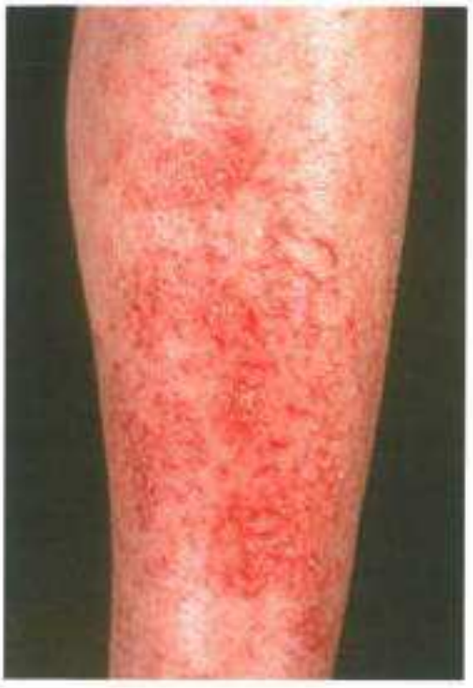


Fig. 4.5 Asteatotic eczema. The elderly are particularly susceptible to this. This eczema is very dry and fissured producing a 'crazy paving' appearance.

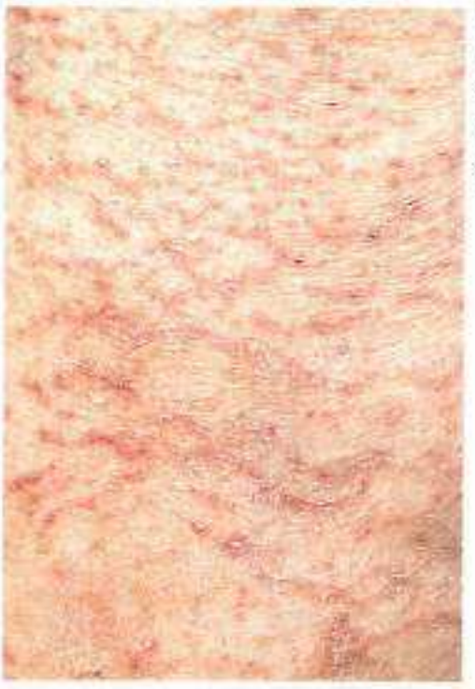


Fig. 4.6 Asteatotic eczema. Sore, dry red cracks occur characteristically on the shins of the elderly, usually as a result of overzealous washing in winter.

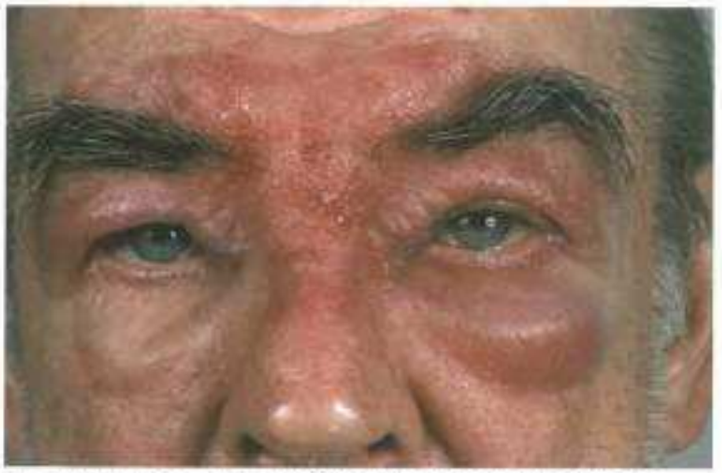


Fig. 4.7 Contact dermatitis. The inflammatory reaction is often acute and vesicular or bullous. The face is often involved secondarily to contact dermatitis elsewhere (autosensitization eczema).

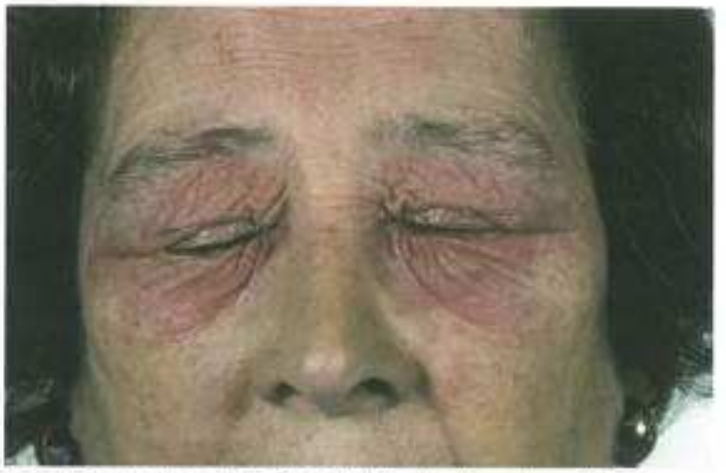


Fig. 4.8 Contact dermatitis. This patient developed an autosensitization eczema around her eyes secondary to contact dermatitis to rubber in her clothing.

particularly as part of autosensitization, which is a reaction of the skin to contact dermatitis elsewhere on the body. An industrial dermatitis is usually on exposed areas of the skin, particularly the hands and arms, and areas that are touched by the hands, for example the face and genitals. The face and eyelids are often also involved if the chemical is volatile.

The particular features of certain common examples of contact dermatitis are described here.

Contact dermatitis from metal

Metal is the commonest cause of contact dermatitis and predominantly affects young females. Nickel and cobalt (a contaminant of nickel) are constituents of costume jewellery (Fig. 4.9) and a host of other items such as spectacle frames (Figs 4.10 and 4.11), zips (Figs 4.12 and 4.13), hairpins, chairs, chains and metal clips. The diagnosis is suspected by the sites involved, viz. earlobes (earrings), cheeks (metal spectacle frames), neck (necklace and/or catch), wrists (bracelet, watch strap), waist and umbilicus (jean studs), elbow (chain on bag), lower leg (zip in boots) and back of thighs (metal chair), but the phenomenon of autosensitization (i.e. an eczema on the face, particularly the eyelids, and the elbow flexures secondary to the primary site of sensitization) may occur.

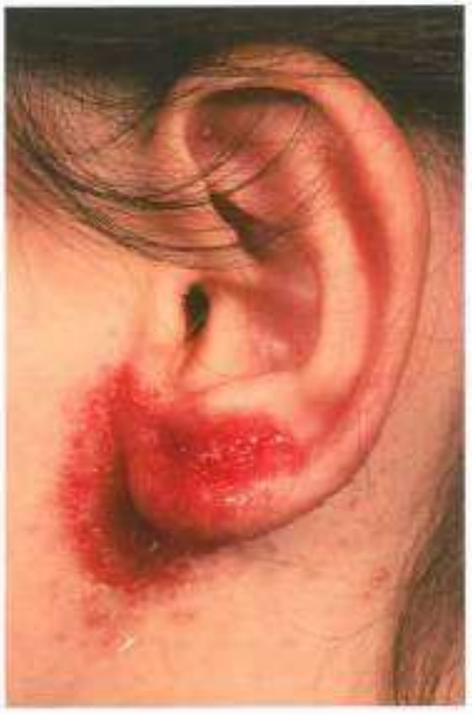


Fig. 4.9 Nickel dermatitis. This lady was sensitive to metal in her earrings. It is the most common form of contact dermatitis in women. It had become secondarily infected in her case.

There has been considerable interest in the relationship between the metal of metal arthroplasties that fail and metal allergy. Approximately two thirds of patients with failed arthroplasties are metal sensitive. Pre-implantation patch testing may help to predict this. Metal–plastic alloys are better tolerated. Cobalt may be released in sufficient quantities from dental plates and fillings to cause a stomatitis (Fig. 4.14).

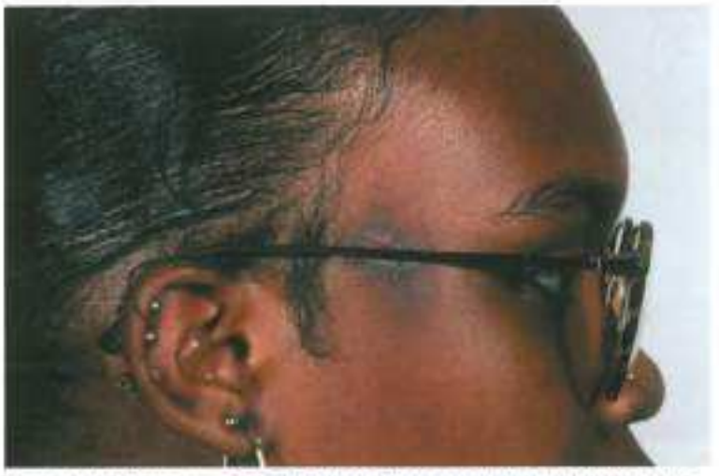
Contact dermatitis from rubber

The allergen is usually a rubber accelerator or antioxidant used in the manufacture of rubber rather than rubber or latex itself (although latex is increasingly recognized as a cause of contact urticaria and potential anaphylaxis). The paraphenylenediamine group of rubber additives are an important cause of industrial dermatitis in those involved in the manufacture of tyres. It is also present in black rubber so may be found in the home in flexes, cables, hoses and grips; squash balls and scuba masks are also common sources. The common sites of rubber dermatitis are hands (gloves, tyres [mechanics]), feet (shoes, especially rubber soles), waist (elastic in underwear), chest (elastic in a brassière), face (bathing cap, snorkel mask or autosensitization) and body (wetsuits).

Rubber gloves are the most frequent allergen (usually positive to thiurams and carbamates on patch testing). The eczema occurs on the backs of the fingers and hands and around the wrists and forearms (where the eruption may be sharply delineated; Fig. 4.15). The palms are often spared, presumably because the allergen has more difficulty penetrating the very thick stratum corneum. Sensitization may occur as a complicating factor in patients who already have a primary irritant or constitutional eczema and use rubber gloves to protect their hands.

Shoe dermatitis is usually caused by the rubber adhesive used to glue the parts together. The dermatitis occurs on the weight-bearing parts of the soles, so the instep is usually spared, and on the dorsa of the feet and toes with sparing on the toe-web spaces. Mercaptobenzothiazole (MBT) is the most frequent allergen. It is also responsible for dermatitis in elastic in clothing (Fig. 4.16) and from elastic bands. The diagnosis of clothing dermatitis is not difficult because the distribution of the eruption corresponds so well to the article of clothing worn. Mercaptomix, thiuram mix, black rubber mix and carbamix are constituents of the standard European battery used in patch testing.

Figs. 4.10 Nickel dermatitis. This young lady presented with a patch of hyperpigmented skin.



Figs. 4.11 Nickel dermatitis. The cause of the pigmentation was secondary to contact dermatitis to her metal spectacle frame.

Contact dermatitis from resins

Epoxy resins are encountered not only in industry but also in glues used as adhesives in the home, in stoma bags, in plastic tubing, spectacle frames and gloves.

Acrylates are also used industrially and in adhesive tapes, spectacle frames, dental resins (see Fig 7.63) and in artificial nails.

Formaldehyde resins, for example phenol formaldehyde resins, are used in industry but paratertiary butylphenol (PTBP) formaldehyde is present in adhesives in shoes, watchstraps, artificial nails and their adhesives, glues and inks. Aminoformaldehyde polymers are present in melamine. The main source of urea formaldehyde resin is industry but it is used in some textiles and may cause clothing dermatitis.

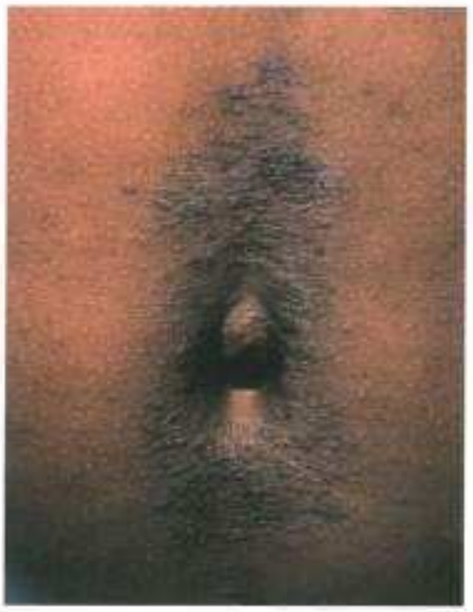


Fig. 4.12 Nickel dermatitis. There are hyperpigmented lichenoid papules above and around the umbilicus. This is a classic site for metal induced allergic contact dermatitis.

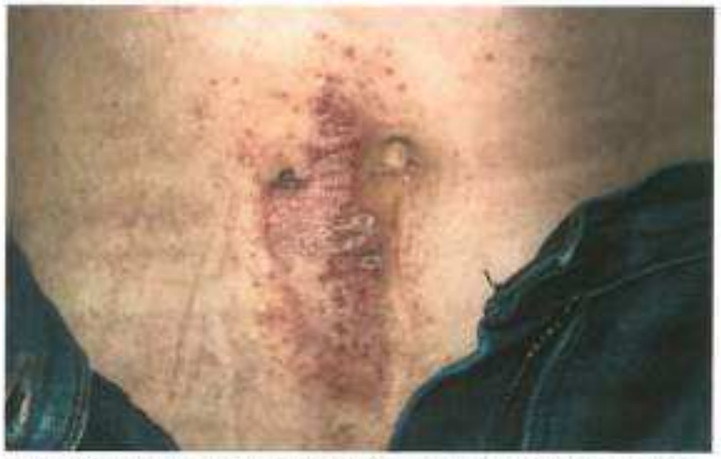


Fig. 4.13 Nickel dermatitis. The wearing of jeans has led to a rise in incidence of eczema around the groin and umbilicus secondary to metal zips and studs. Clothing between the metal and the skin does not prevent the allergic reaction.

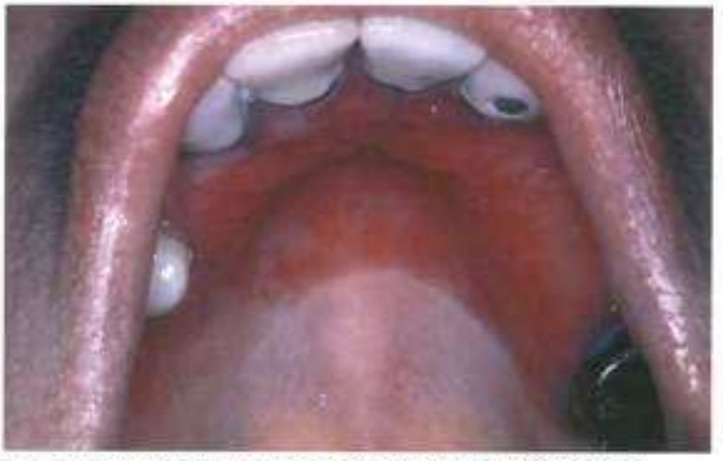


Fig. 4.14 Metal plate dermatitis. The dermatitis is very well defined and corresponds to the position of her metal plate. Patch testing was positive.

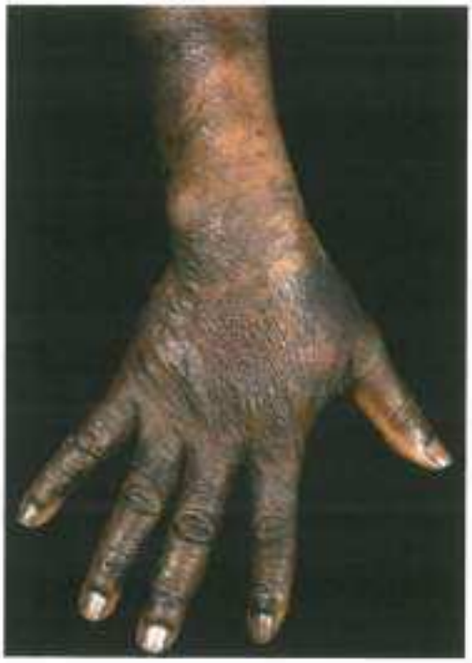


Fig. 4.15 Rubber glove dermatitis. The dermatitis occurs around the wrists, forearms and backs of the hands. The palms are involved to a much lesser extent, probably because of their thickness.

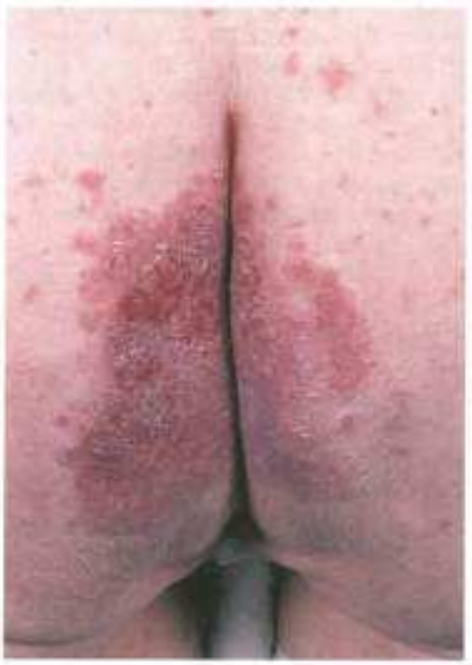


Fig. 4.16 Rubber dermatitis. Rubber is present in elastic in clothing including underclothing. Sensitivity usually develops in middle age.

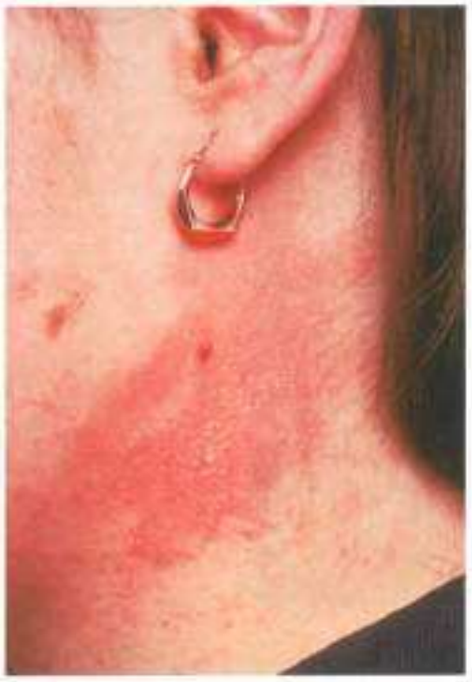


Fig. 4.17 Contact dermatitis. Perfume dermatitis occurs at the sites of application and in particular on the neck.

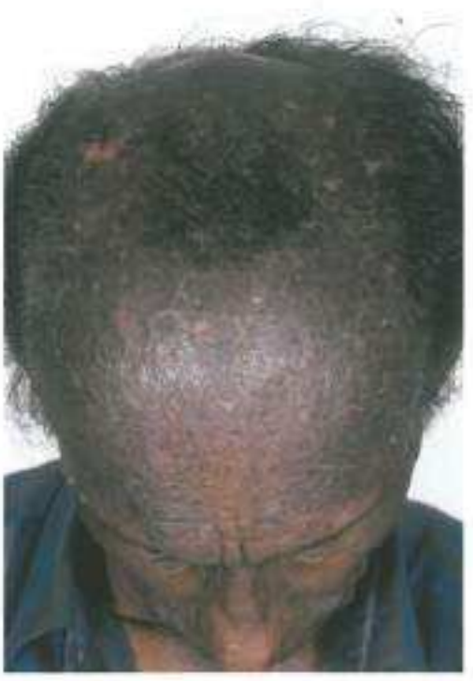


Fig. 4.18 Hair dye dermatitis. The dermatitis is acute and may lead to temporary hair loss. Postinflammatory hyperpigmentation and excoriation is prominent here, where the causative agent is paraphenylenediamine.

Contact dermatitis from clothing

Metal in clothes, particularly jeans, button fasteners, hooks in brassières and zips and ornamental attachments in boots and shoes is the commonest cause but dyes and formaldehyde resins (added to produce crease-resistant finishes) may produce a clothing dermatitis. Sweat may leach out the allergens, and moisture, occlusion and friction aid their penetration. The eruption is usually seen first around the axillae, sparing the vault, and then the elbow flexures, inner thighs, lower legs and neck, i.e. those areas most in contact with clothing. During World War II, a purpuric lichenoid contact dermatitis was seen secondary to wearing khaki uniforms.

Stocking dermatitis is caused by azodyes (which may cross-react with paraphenylenediamine) and the eruption is seen primarily at the sites of closest contact, for example the inner thighs, popliteal fossae and feet. Patch testing to Disperse yellow and Disperse orange and to the stocking should be performed.

Shoe dermatitis is most common in the Third World. The pattern of the dermatitis depends on whether the uppers or the sole of the shoe is responsible. If the problem lies with the uppers, the dorsa of the toes, with sparing of the toe webs, and the feet (from the tongue of the shoe) are affected. If it is caused by the soles, the weight-bearing areas are affected; however, the whole foot may be involved in sports shoes, which are moulded to fit the weight-bearing areas as well as the instep. Shoe dermatitis is usually caused by leather, rubber, glues, dyes or impregnated linings. Chromates or glutaraldehyde is used to tan leather, particularly in countries other than the UK and the USA. In the latter, rubber, particularly MBT, is the most common cause. Latex adhesives used to stick the sole to the upper, PTBP formaldehyde resin and colophony are other allergens used in the glueing process. In order to prevent mildew, substituted phenols or organic mercury are impregnated in the linings of the shoes and some patients do sensitize to these. Hydroxyacids in sweat liberate chromate from leather easily and patients with hyperhidrosis or living in humid climates are susceptible; those who wear certain types of Indian sandal may also be affected.

Contact dermatitis from chromates

Contact dermatitis caused by chromates is becoming less frequent, probably because increased mechanization has reduced exposure to cement, which is the commonest cause of chromate dermatitis, and also the addition of ferrous sulphate has reduced its sensitizing potential. It often becomes a chronic dermatitis because the patient is unwilling to give up working. The eruption is mainly seen on the backs of the hands, but the palms may be involved. If the feet are involved and the patient is allergic to chromates on patch testing, this suggests a dermatitis to chromates in leather.

Contact dermatitis from perfumes and cosmetics

Cosmetics rarely cause allergic contact dermatitis considering how extensively they are used. Many act as irritants rather than true allergens, particularly in atopics.

Perfumes are the most common allergens and the dermatitis occurs at the site of application, usually the neck (Fig. 4.17) and wrists, and on the face from the perfume sprayed into the atmosphere. However, many substances are perfumed and the dermatitis may occur on the hands from perfumed soap or in the axillae from perfumed deodorants (these also contain formaldehyde). Because the axillae are occluded areas and permit enhanced penetration, sensitization is frequent. Fragrance mix is the test allergen used but Balsam of Peru, colophony and wood tars are also markers of perfume sensitivity.

Hair dyes (e.g. paraphenylenediamine) occasionally sensitize, and this is usually acute on the forehead (Fig. 4.18), tips of the ears (Fig. 4.19) and around the neck (Fig. 4.20). They may even produce an acute swelling around the eyes which may be mistaken for angioedema. Postinflammatory hyperpigmentation may be marked (Fig. 4.21). Dyes are also present in clothing but do not produce problems as frequently as they used to.

Preservatives are added to creams to prevent bacterial contamination. These bacteria may be pathogens or cause discoloration, malodour and degradation of the product. Parabens, imidazolidinylurea, quaternium 15, formaldehyde and methylchloroisothiazolinone are common examples. Many preservatives are more likely to sensitize if the skin is already slightly damaged.

Para-aminobenzoic acid (PABA) is an ingredient of some sunscreens and may produce either an allergic contact or a photocontact dermatitis.

Lipsticks do not often produce a contact dermatitis. In the past, when it occurred, the agent was most likely to be eosin, but most of the impurities that were responsible for the dermatitis have now been removed. Oils, waxes and antioxidants are the most likely sensitizers. Flavourings in toothpaste may cause a dermatitis on the lips and even burning stomatitis in the mouth. Metal pins and keys held in the mouth may produce a contact dermatitis on the lips.

Contact dermatitis from nail varnish

Nail varnish dermatitis is often not suspected, because the eruption occurs at the sites of the contact with nail varnish – face, neck (Fig. 4.22), jaw and upper chest (Fig. 4.23) – rather than around the fingernails as might be assumed. This is because women apply the nail varnish carefully to the nails (which do not react), without touching the surrounding skin. The eruption, like other forms of contact dermatitis, may be acute or subacute, sometimes causing closure of the eyes and swelling of the face. Often, oval patches corresponding to the fingernails are clearly seen on the cheeks or jaw. The allergen is santolite (aryl-sulphonamide formaldehyde).

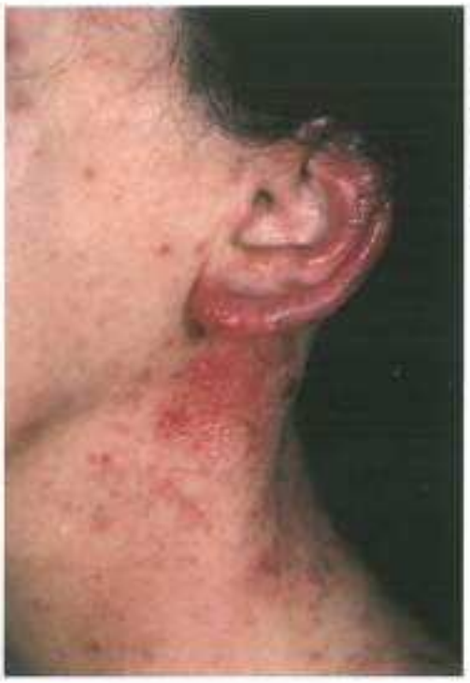


Fig. 4.19 Hair dye dermatitis. There is an acute erythematous vesicular dermatitis affecting the ears and neck. The scalp hair is unnaturally dark for a fifty year old which may suggest the diagnosis.

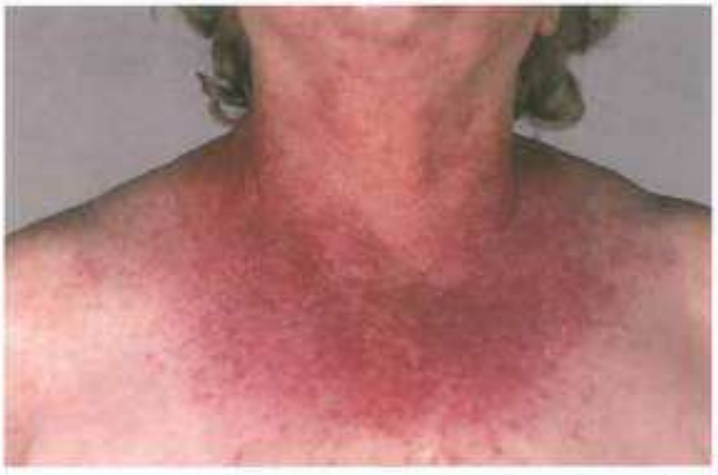


Fig. 4.20 Hair dye dermatitis. There is an extensive acute dermatitis. Patch tests are invaluable in elucidating the cause of such a reaction.

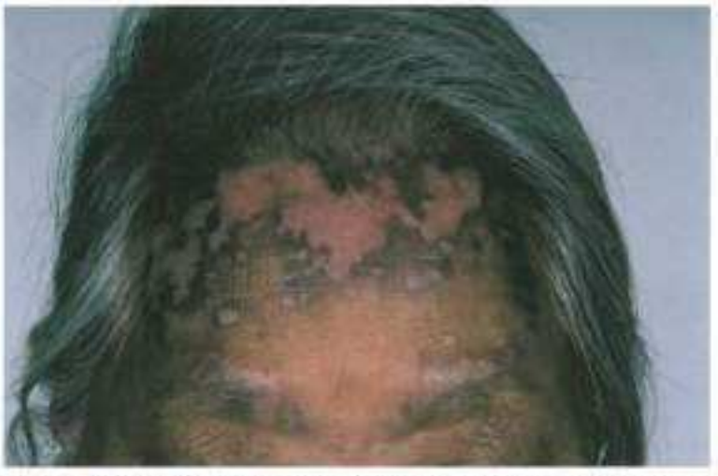


Fig. 4.21 Hair dye dermatitis. The allergic reaction to paraphenylenediamine is usually acute with weeping and oedema. Postinflammatory hyperpigmentation may be marked and take months or longer to clear.

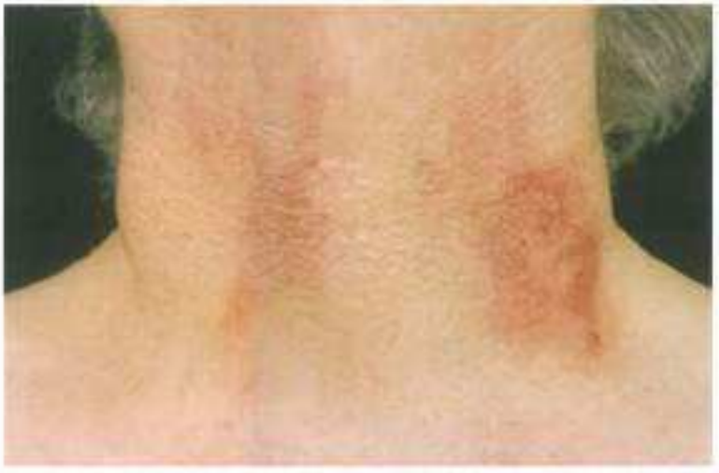


Fig. 4.22 Nail varnish contact dermatitis. The dermatitis occurs at sites touched by the nail varnish but not on the nails themselves.

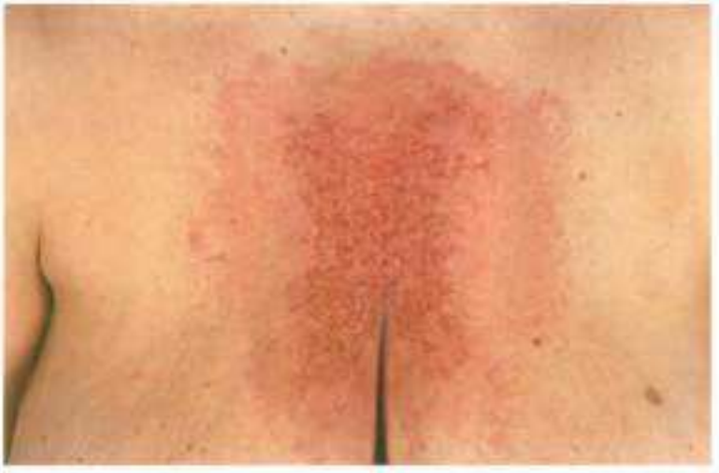


Fig. 4.23 Nail varnish contact dermatitis. The dermatitis is often acute and weeps. The front of the chest is a common site.

Contact dermatitis from medicaments

Local anaesthetics and topical antihistamines are common causes of *dermatitis medicamentosa*. Dermatologists rarely use either for that reason. Local anaesthetics are often present in creams prescribed for pruritus ani (Fig. 4.24). Benzocaine is the commonest. It is an ester of PABA and will cross-react with sunscreens containing it, but there is no cross sensitivity with lidocaine, which belongs to the amide group of local anaesthetics and rarely sensitizes. Topical antihistamines are available over the counter for itchy eruptions, including insect bites. They are of no proven value and are best avoided. Lanolin is gradually being removed from many face creams as it is a well-recognized sensitizer, but it is still a common constituent of moisturizers and may cause dermatitis (Figs 4.25 and 4.26). Ethylenediamine was present in Triadcortyl (Mycolog) as a stabilizer and was a frequent allergen.

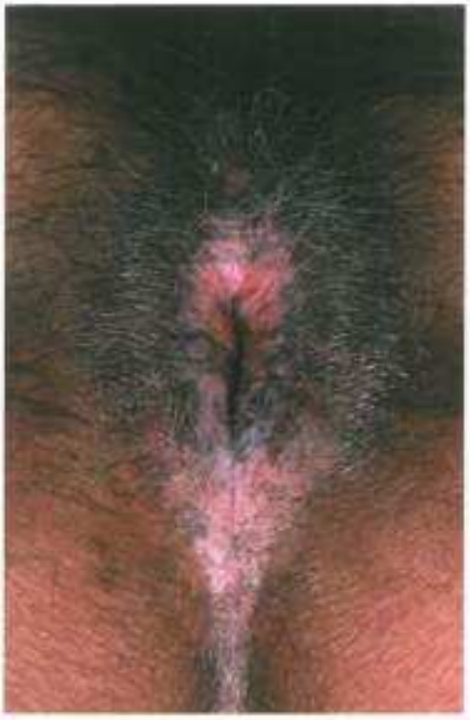


Fig. 4.24 Dermatitis medicamentosa. Certain sites are more prone to contact dermatitis including the perianal area to local anaesthetics and perfumed materials.

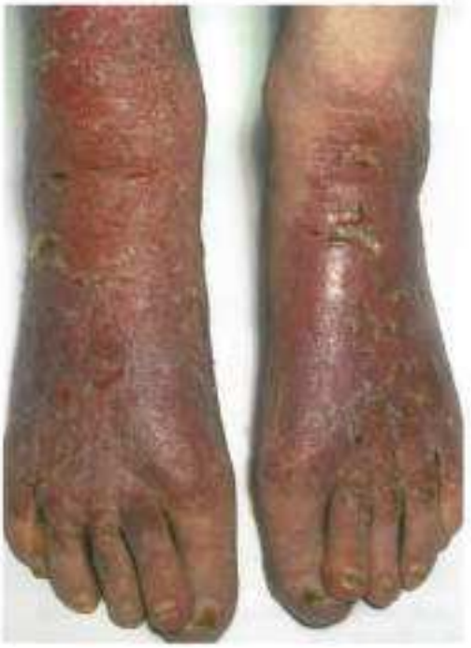


Fig. 4.25 Dermatitis medicamentosa. Preservatives, lanolin and neomycin are amongst the commonest causes of contact dermatitis on the legs, particularly in association with varicose eczema.

Topical antibiotics, such as neomycin and its cross-reactants soframycin and framycetin, may sensitize when prescribed for perianal conditions, ophthalmological disorders, gravitational eczema (Figs 4.27 and 4.28) and ulcers and otitis externa (Fig. 4.29) (a form of seborrhoeic dermatitis affecting the ears). Why these sites are vulnerable is not known. Topical antibiotics are also used in combination with topical steroids, but sensitization is unusual, except in the case of varicose eczema. The diagnosis should be suspected if an eczematous eruption, which ordinarily would respond to such a preparation, deteriorates. Considering its widespread use, chloramphenicol used in eyedrops rarely sensitizes.

Contact dermatitis to topical steroids (Fig. 4.30), although uncommon, should be considered if a steroid-responsive dermatosis deteriorates. Patch testing is to tixocortal pivalate, a marker for hydrocortisone, budesonide and hydrocortisone 17 butyrate sensitivity.

Tattoo reactions

Zirconium, beryllium, mercury (red), chromium (green) and cadmium (yellow) are the common pigments used for tattooing and may produce a contact dermatitis after several years (Fig. 4.31). The inflammatory response is granulomatous. Excision of the tattoo solves the problem.

Phosphorus sesquisulphide (match) dermatitis

Phosphorus sesquisulphide is a constituent of 'strike anywhere' non-safety matches and is present in the striking head of the match and the strike side of the box. It is rarely suspected by the patient (usually male). The outer thigh (Fig. 4.32) or breast are affected from the trouser or shirt pocket in which the matches are kept and the face is involved from the fumes (Fig. 4.33). The palm of the hand may be involved from holding the box. The condition will flare up wherever such matches are used.

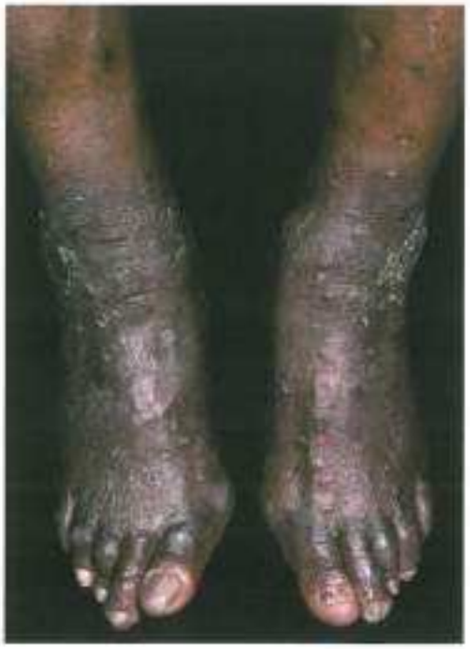


Fig. 4.26 Dermatitis medicamentosa. The erythema of dermatitis is less obvious in black skin than in white (Fig. 4.25). Postinflammatory hyperpigmentation predominates but vesicles and crusting are present.

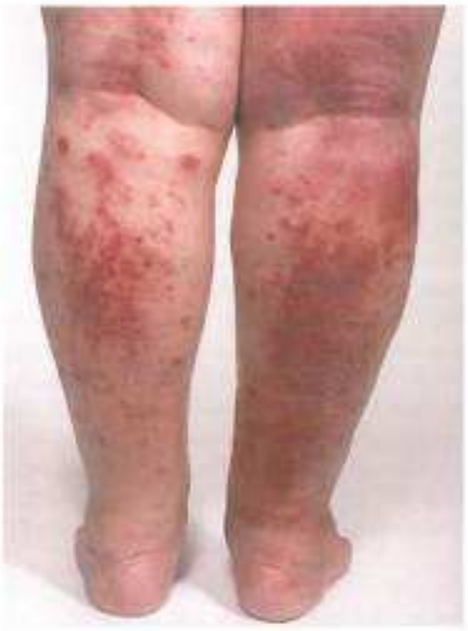


Fig. 4.27 Contact dermatitis and autosensitization. This 50-year-old lady sensitized to the neomycin in her steroid antibiotic cream used to treat her varicose eczema.

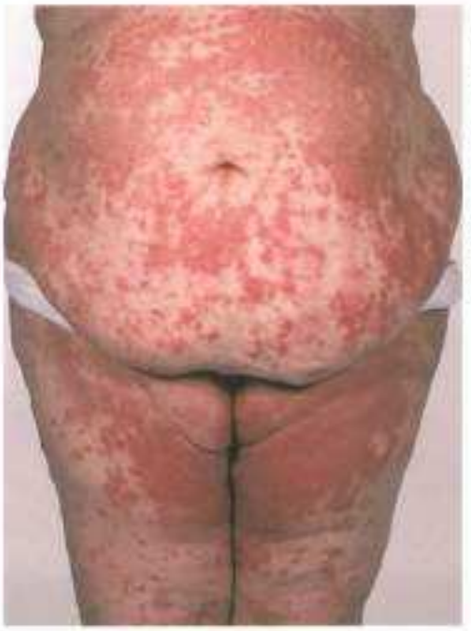


Fig. 4.28 Contact dermatitis and autosensitization. The dermatitis (see Fig. 4.27) spread to areas not treated with the cream, which included the trunk and face. This may often become erythrodermic if the allergen is not discontinued.

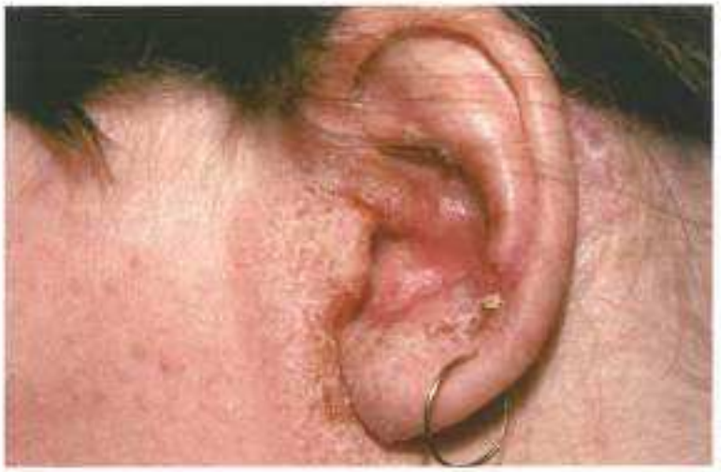


Fig. 4.29 Dermatitis medicamentosa. This patient suffered from otitis externa and developed a reaction to the gentamycin in her steroid/antibiotic cream.

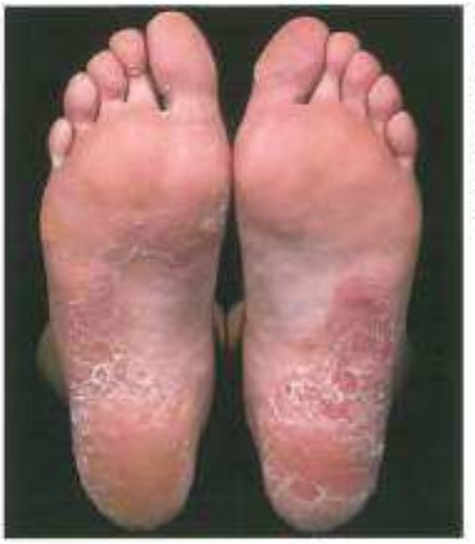


Fig. 4.30 Contact dermatitis. This patient's eczema was not responding. Patch testing showed her to be allergic to tixocortol pivalate, a marker for certain topical steroids. It cleared on stopping hydrocortisone 17-buyrate.

Fig. 4.31 Tattoo contact dermatitis. This patient developed a reaction to the cinnabar (red) dye in his tattoo. Excision is the only successful treatment.

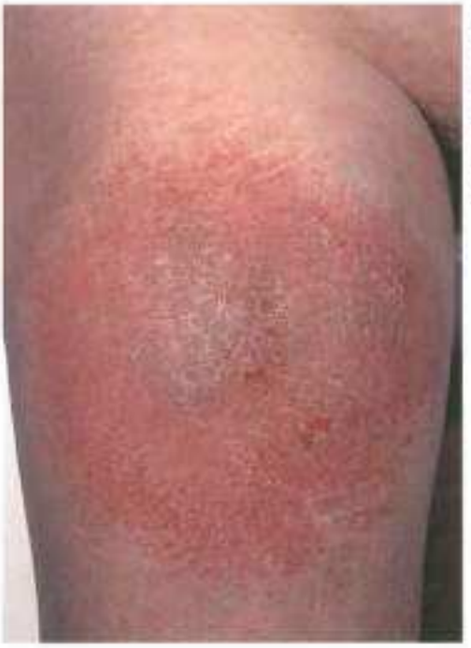


Fig. 4.32 Phosphorus sesquisulphide dermatitis. This patient kept his matches in his trouser pockets. Note how acute the reaction is, a feature of contact dermatitis

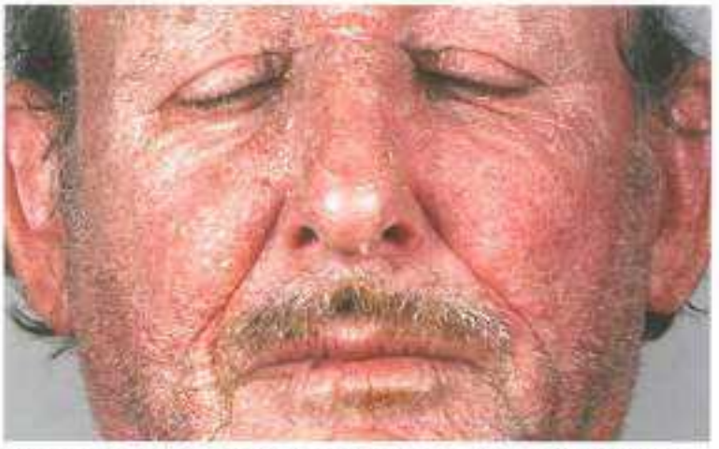


Fig. 4.33 Phosphorus sesquisulphide dermatitis. The dermatitis occurs on the face from the fumes and at sites where the matchbox is close to the skin.

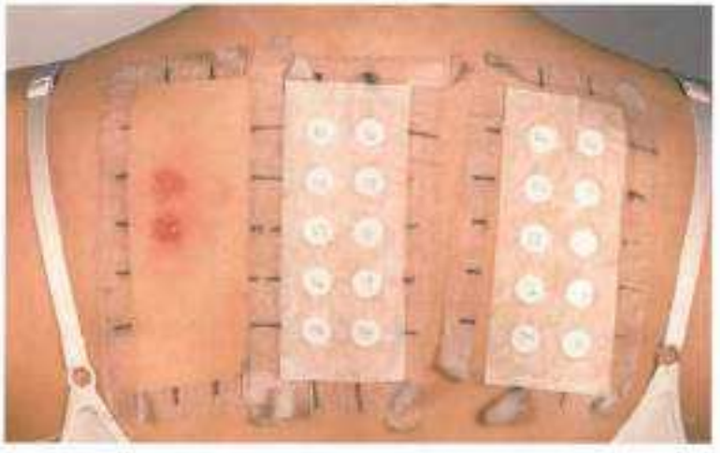


Fig. 4.34 Patch tests. A battery of common and suspected allergens are applied to the back. The skin is examined at 48 and 96 hours. Irritant reactions disappear, allergic ones do not. Two positives are present.

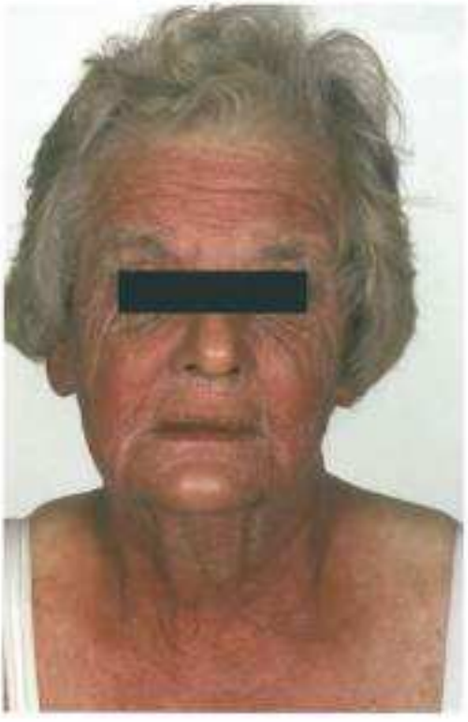
Management

The diagnosis should be confirmed by patch testing. There are approximately 40 allergens that are encountered frequently enough to constitute a battery to which other relevant potential allergens are added, for example parts of the shoe if a foot eruption is being investigated, and the patient's cosmetics and nail varnish if a facial dermatitis is under review. The chemicals are put into aluminium wells fitted into an adhesive tape and then applied to the patient's back. They are removed after 48–72 hours, and the skin is inspected for a patch of dermatitis corresponding to the application site of the allergen (Fig. 4.34) and re-examined 48 hours later. It requires experience because irritant reactions may occur and is normally done by the dermatologist. Irritant reactions always happen, for example, if shampoos are patch tested. An irritant reaction disappears by the second reading, whereas an allergic reaction will still be present. Some physicians suggest that all patients with eczema should be patch tested because clinical acumen is not always accurate, but this is not always practical and there is danger of sensitizing a patient to an allergen during the procedure. Its advantage is that it demonstrates to both the patient and the doctor the cause of the dermatitis.

Clearly, the patient will recover if the antigen is permanently removed. Sometimes a substitute may be used (e.g. santolite-free nail varnish and fragrance-free cosmetics). Nickel dermatitis can be difficult because some patients find metal adornments hard to give up. It is important to tell them that clothing between the metal and the skin does not prevent the reaction because sweat leaches out the metal. Painting the metal with nail varnish is also unsatisfactory as it quickly wears off.

Patients with rubber sensitivity should be advised to change to polyvinyl chloride (PVC) gloves, preferably lined with cotton, and all-leather, canvas or PVC shoes. Elastic in underwear should be removed; lycra brassieres are recommended. Other sources of rubber (e.g. squash balls, tyres and rubber undersheets and pillows) should be identified.

Contact dermatitis responds to potent steroids on the body and 1% hydrocortisone ointment for the face; Figs 4.35 and 4.36). It will not be cured, however, until the allergen is identified and avoided. Systemic steroids starting with prednisolone 30 mg daily and reducing by 5 mg every fourth day are indicated in severe cases.



Figs 4.35 Contact dermatitis. This patient developed contact dermatitis to rubber in her elastic stocking. The facial eczema resulted from autosensitization.

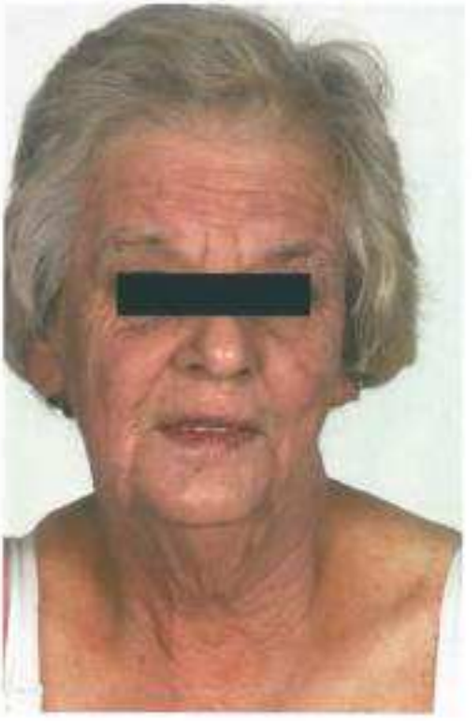


Fig. 4.36 Contact dermatitis. The facial eczema (Fig. 4.35) responded to hydrocortisone ointment within 48 hours (Fig. 4.36).

Plant contact dermatitis

A delayed hypersensitivity allergic contact reaction to a plant.

Aetiology

The plants responsible vary depending upon the local flora. The most common in North America are members of the genus *Rhus*, especially poison oak and ivy (Fig. 4.37). In the UK, although ivy occasionally causes a contact dermatitis, primula (Fig. 4.38) is the most common and is caused by a quinone (primin) in the hairs on the leaves, stems and flowers. Chrysanthemums and other *Compositae* contain sesquiterpene lactones in their stems and leaves which may sensitize florists and gardeners. Tulip, garlic and onion bulbs contain a natural fungicide, α-methyl-μ-butyrolactone, which produces dermatitis on the fingertips. Airborne contact dermatitis may result from some species, for example the American ragweed Ambrosia. In India, there is an epidemic from the weed *Parthenium hysterophorus* imported unwittingly from Texas.

Clinical Features

These depend on the source. *Primula* and *Rhus* sp. cause an acute dermatitis that is either papulovesicular (Fig. 4.39) or vesiculo-bullous (Fig. 4.40) in morphology and streaky and patchy in configuration. The areas affected are the fingertips and hands, forearms and areas touched by fingers, e.g. face (especially eyelids) and genitalia. Bulb dermatitis is a chronic dry hyperkeratotic eczema of the fingertips and under the nails, whereas chrysanthemum dermatitis is a chronic lichenified eczema of the exposed parts, simulating an airborne contact dermatitis.

Management

Patch testing

This establishes the diagnosis. Avoidance of the allergen(s) prevents recurrences.

Steroids

Potent topical steroids are helpful. In acute cases (e.g. poison ivy dermatitis) systemic steroids may be required.

Fig. 4.37 Poison ivy. This is the commonest plant allergen in the USA. It produces an acute vesiculo-bullous dermatitis and often requires treatment with systemic steroids. (Courtesy of Dr C.R. Lovell.)

Fig. 4.38 *Primula obconica*. This is the most common cause of plant dermatitis in the UK. Other primulae are usually safe.

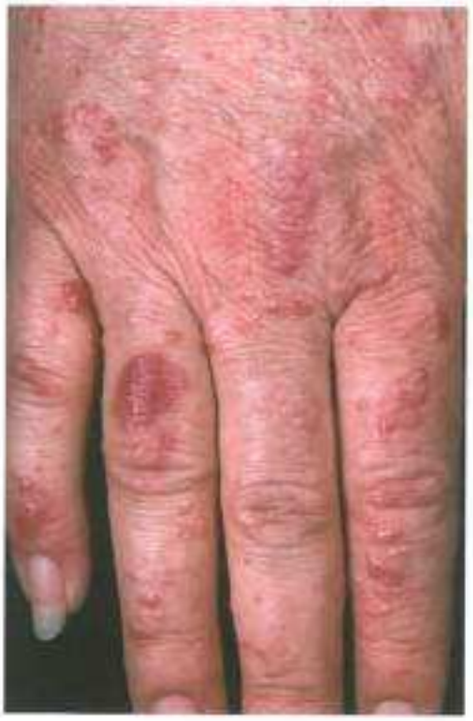


Fig. 4.39 Contact dermatitis to primula. A vesicular or bullous eruption occurs on the fingertips and those areas of the body touched by the contaminated fingers, notably the face.

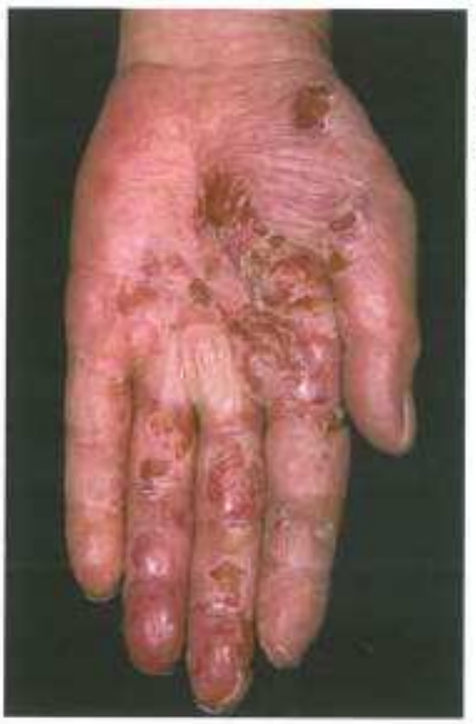


Fig. 4.40 Contact dermatitis to primula. This man developed a dermatitis on his hands from tending his primula plant. The allergen is primin in the hairs on the stems, leaves and flowers.

Phytophotodermatitis

A reaction between a plant chemical and ultraviolet light, resulting in acute blistering and pigmentation.

Aetiology

The chemical causing phytophotodermatitis is a furocoumarin containing 5-methoxypsoralen, which is brushed onto the skin, commonly either by lying in a meadow or by cutting back weeds on a summer's day. The direct interaction between long-wave ultraviolet light and the psoralen causes an inflammatory reaction to take place. The main plants responsible are parsnips, giant hogweed, cow parsley, dill, angelica, fennel, celery, *Ammi majus*, lime, bergamot and orange. *A. majus*, which grows along the Nile valley, has been known for centuries in Egypt as a phototoxic agent and is used to treat vitiligo. It contains a psoralen that is now used to treat psoriasis as part of photochemotherapy (PUVA).

Clinical Features

Symptoms

Pruritus and pigmentation.

Morphology

The degrees of inflammatory response vary, but it is usually vesiculobullous (Figs 4.41 and 4.42) and is always followed by postinflammatory hyperpigmentation, which consists of a bizarre network of streaks (Fig. 4.43) so characteristic as to constitute a spot diagnosis.

Distribution

The reactions occur at the site(s) of exposure.

Management

A potent topical steroid may be indicated in the acute stages, but explanation is usually all that is required. The postinflammatory hyperpigmentation does take several weeks or months to clear, depending on the skin type.

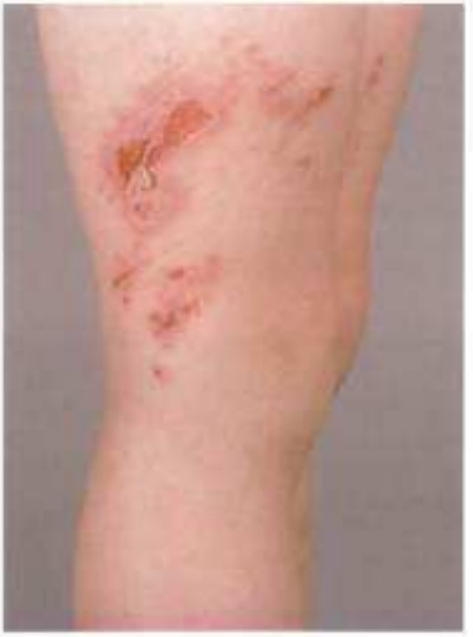


Fig. 4.41 Phytophotodermatitis. A bizarre streaky vesiculobullous eruption occurs on sites which have been in contact with weeds containing furocoumarins and which have interacted with sunlight.

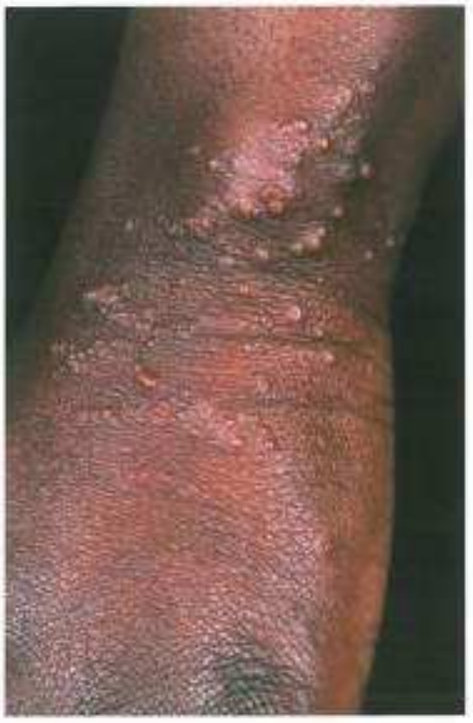


Fig. 4.42 Phytophotodermatitis. There are many vesicles but it is their linear arrangement that suggests the diagnosis of a plant-induced phototoxic reaction.

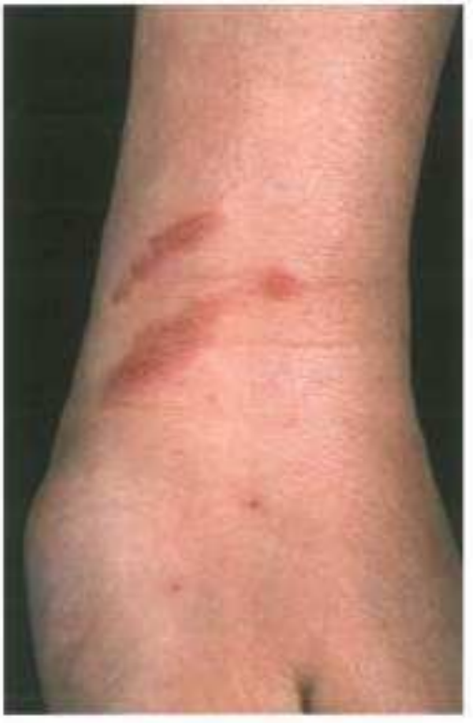


Fig. 4.43 Phytophotodermatitis. The acute reaction may be over by the time the patient presents and there is only linear hyperpigmentation to be seen. If a proper history is taken the diagnosis should become clear.

Photoallergic contact dermatitis

A delayed hypersensitivity, cell-mediated immunological response to the combination of an allergen and ultraviolet light; it only occurs in predisposed individuals.

Aetiology

The skin requires to be primed and subsequently re-exposed to the allergen. The sensitivity is lifelong and the dermatitis will recur every time the patient is exposed to the chemical and sunlight.

The best known example of this problem occurred in the 1950s. Certain bacteriostatic substances, namely tetrachloro- (or bromo-) salicylanide, were added to toiletries and soaps (Lifebuoy in particular). The dermatitis occurred on exposed areas of the skin on bright sunny days when there were still traces of the chemical from the soap on the skin. This was a true photoallergic contact dermatitis. The condition is no longer encountered in the UK, but occasionally small epidemics of cases occur when the chemical is added to soaps by manufacturers who are unfamiliar with its chemistry. Bithionol and hexachlorophane occasionally cause a similar problem.

It occurred again in the 1980s when a scent containing musk ambrette was added to aftershave preparations and colognes and a photocontact dermatitis occurred on exposed areas, particularly the face. Balsam of Peru is similarly a potential photosensitizer. Plant derivatives such as sesquiterpene lactones (from *Compositae*) and certain woods (pine, teak, birch and spruce) also photosensitize.

When applied to the skin, topical medicaments containing sulphonamides and promethazine may act as photocontact allergens, but as there is no need to prescribe them the problem should not really occur. Systemic agents occasionally cause photocontact dermatitis through sensitization by a topical route, particularly in workers manufacturing drugs such as phenothiazines and in patients taking, for example, promethazine hydrochloride or sulphonamides.

The most common photoallergens currently are the ultraviolet-absorbing chemical sunscreens, particularly PABA, oxybenzone, benzophenones and methoxycinnamates.

Clinical Features

Symptoms

An itching rash occurs.

Morphology

The eruption is mainly eczematous.

Distribution

Photoallergic contact dermatitis occurs on exposed parts of the skin such as the face, 'V' of the front of the chest, backs of the hands (Fig. 4.44) and, in women, the lower legs. Areas protected from sunlight are spared (Fig. 4.45) (e.g. behind the ears, under the eyebrows, the nose, the chin and the hair).

Management

Photopatch testing

Most of the chemicals are only allergenic once irradiated, usually with ultraviolet A. Photopatch tests are performed in duplicate; at 48 hours after reading them, one set is irradiated with UVA, usually at 50% of the minimal erythema dose. The test is considered positive if the irradiated side reacts and the non-irradiated does not. Occasionally ultraviolet B irradiation of the patch test is necessary. The allergen must be avoided for life because these patients may become persistent light reactors and develop *chronic actinic dermatitis* (formerly known as *actinic reticuloid*) despite subsequently avoiding the photoallergen.

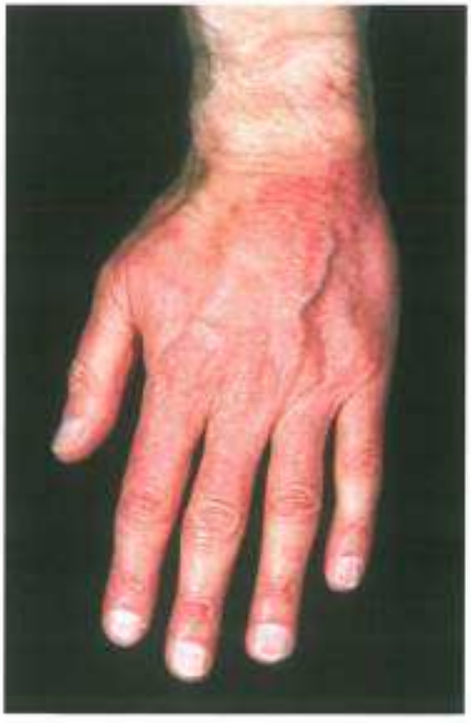


Fig. 4.44 Photocontact dermatitis. The exposed skin such as the backs of the hands are affected. There is a sharp cut off from the normal skin covered by the shirt sleeves.

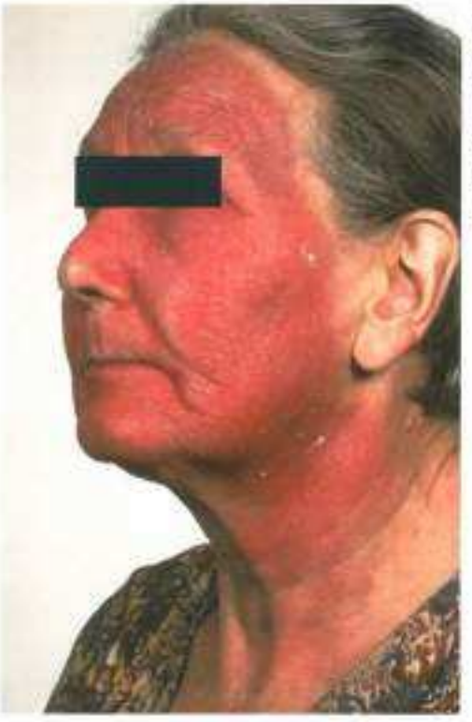


Fig. 4.45 Photocontact dermatitis. This occurs on those areas of skin exposed to ultraviolet light irradiation. Note sparing of the skin which had been protected by hair and the skin on the underside of the nose.

Berloque dermatitis

An interaction between bergamot in colognes and perfumes and long-wave ultraviolet light, resulting in postinflammatory pigmentation.

Aetiology

This has a similar mechanism to phytophotodermatitis but is caused by an interaction between oil of bergamot, which contains 5-methoxypsoralen, and long-wave ultraviolet light. Oil of bergamot is present in many colognes and perfumes.

Clinical Features

Symptoms

The acute inflammatory stage of Berloque dermatitis may not occur and instead the patient presents with a pigmentary problem.

Morphology

A bizarre streaky hyperpigmentation can be seen.

Distribution

Wherever the perfume has come into contact with the skin, but the side of the neck is most typical (Fig. 4.46).

Management

Explanation is usually sufficient. The pigmentation slowly fades after a number of months.

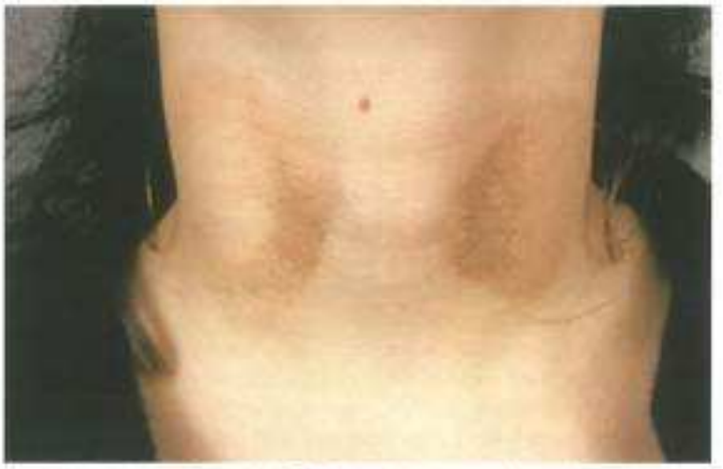


Fig. 4.46 Berloque dermatitis. This dermatitis is caused by an interaction between sunlight and oil of bergamot, which is present in many perfumes. The side of the neck is the commonest site.

Psoriasis 5

Psoriasis is a common chronic benign hyperproliferative and autoimmune disorder driven by activated memory T cells which secrete cytokines that induce keratinocyte and vascular changes including increased proliferation and decreased cellular maturation. Keratinocytes, dendritic cells and monocytes also produce other cytokines which magnify these effects. It is often inherited and sometimes associated with disorders of the joints and nails. It is generally characterized by symmetrical, well-defined, red plaques with a thick silvery scale, but there are a number of morphological variants.

Aetiology

Psoriasis affects 1–2% of Britons, Europeans and North Americans, and both sexes equally. No race is exempt, but whereas it is common in the Indian subcontinent it is rare in West Africans, and hence also in African-Americans and Afro-Caribbeans. It is unusual in Latin American Indians, the Japanese and the Chinese.

One-third of patients recall a family history. Psoriasis is most probably inherited as an autosomal dominant with incomplete penetrance. It is three times more common in monozygotic than in dizygotic twins, but the absence of 100% concordance points to the importance of environmental factors. It may commence at any age from infancy (napkin or diaper psoriasis) to old age, but there are two main peaks, one in youth and the other in late middle age. The early peak is often associated with a positive family history, and siblings are three times as likely to have the disorder as those who develop it in later life. HLA-Cw6 is the most common association, increasing the risk tenfold, but HLA-B27 is positive in pustular psoriasis and arthritis.

Psoriasis may develop in sites of trauma, such as a scratch mark (Fig. 5.1), injury or a surgical incision, sunburn (Fig. 5.2) as a result of friction from tight-fitting clothing or obesity or from irritants (e.g. napkin psoriasis). This is known as the Koebner phenomenon. It occurs 7–14 days after injury in a third of patients. It is probably a marker for a subgroup who have a tendency for earlier onset of psoriasis and early relapse following treatment. A reverse Koebner phenomenon (clearing of existing psoriasis after injury) occasionally occurs.

A streptococcal infection, particularly of the throat, may precipitate guttate psoriasis. It has been proposed that part of the psoriatic genotype is protective against death during epidemics of streptococcal infections but at the expense of increased streptococcal carriage and predisposition to psoriasis in a similar way that sickle cell disease is protective against malaria. The risk of developing psoriasis is increased threefold with human immunodeficiency virus (HIV) infection, and pre-existing psoriasis can deteriorate. The effect of other infections is less well established.

Nicotine, alcohol, antimalarials (sometimes) and lithium (always) may exacerbate the disease. Practolol, a β-blocker now withdrawn, produced an eruption that had several psoriasiform features. The rapid withdrawal

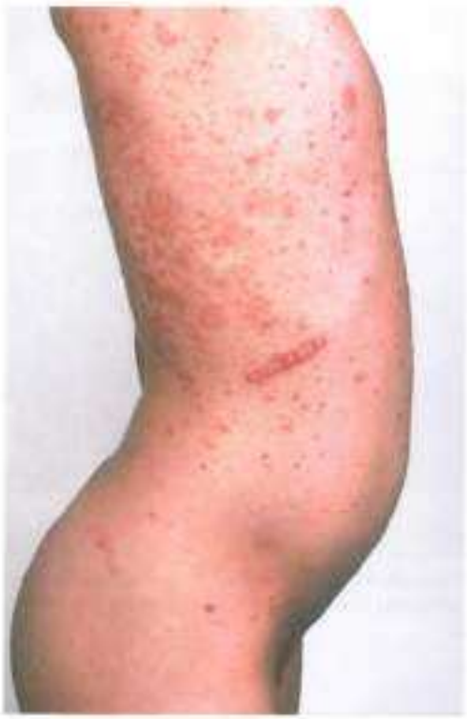


Fig. 5.1 Koebner phenomenon. This child has psoriasis. There is a prominent linear red, scaly plaque on the side of her torso. It was secondary to injury, in this case a scratch.

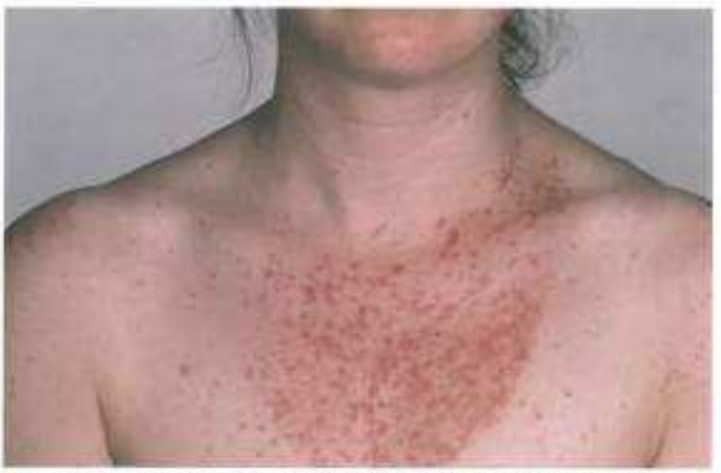


Fig. 5.2 Koebner phenomenon. There is psoriasis in the V of the front of her chest secondary to sunburn. Although ultraviolet light is used to treat psoriasis, it may have a paradoxical deleterious effect.

of steroids (both systemic and superpotent topical) and other immunosuppressives may result in a rebound deterioration of psoriasis and the induction of generalized pustular psoriasis. Localized pustular psoriasis of the palms and soles is more common in smokers. Patients with extensive, subacute, flexural or acral psoriasis often misuse alcohol and improve after months of abstention or significant reduction.

The effects of pregnancy are variable. In general most patients improve, but half of them subsequently deteriorate. Very rarely, generalized pustular psoriasis occurs in pregnancy. Hypocalcaemia, either secondary to parathyroidectomy or during dialysis, may precipitate psoriasis. Usually dialysis improves psoriasis.

Co-morbidities for psoriasis include arthritis, cardiovascular disease, hypertension, obesity, diabetes mellitus, smoking, alcohol misuse and depression. Obese patients with psoriasis are more difficult to treat.

Although many benefit from ultraviolet (UV) irradiation – which may explain the improvement in summer – not all do, and sunburn may produce a Koebner phenomenon. X-irradiation has been used to treat localized psoriasis, but the disease may occur in irradiated skin, particularly when given synchronously with certain chemotherapeutic agents (radiation enhancement).

Psoriasis is characterized by marked epidermal hyperproliferation, and this was the original focus of research. However, it is now generally accepted that this is secondary to and orchestrated by 'cross-talk' between T lymphocytes and the epidermis and dermis via cytokines. Increased numbers of $CD4^+$ (helper) T lymphocytes are present in evolving psoriatic plaques and diminished in resolving lesions, where $CD8^+$ (suppressor) T cells predominate. Cytokines such as interferon-γ (IFN-γ), tumour necrosis factor-α, interleukin 8 (IL-8) and transforming growth factor-α (TGF-α) are present in psoriatic plaques. IFN-γ indicates the presence of activated $CD4^+$ cells. IL-8 and TGF-α stimulate keratinocyte proliferation. Ciclosporin is a relatively selective immunosuppressive but is not an antiproliferative agent that suppresses production of IFN-γ and IL-2 by $CD4^+$ cells and subsequent T lymphocyte proliferation; it is effective in psoriasis as are tacrolimus and anti-CD4 monoclonal antibodies. It seems that T lymphocytes migrate from the peripheral vasculature and enter the skin by a process known as cutaneous leucocyte trafficking. This requires adhesion molecules and their ligands on lymphocytes and other leucocytes to participate in endothelial leucocyte interactions in the skin. Selectins form one group of molecules, responsible for the initial rolling, margination and transient binding of leucocytes to the endothelium of the postcapillary venules, where the blood flow is slowest. Integrins and immunoglobulin superfamily members, such as intercellular adhesion molecule 1, finally arrest the leucocytes and facilitate their transendothelial diapedesis, thus enabling $CD4^+$ T cells to begin their dialogue with the epidermis.

Histology

The histopathology of the chronic stable variant is characteristic (Figs 5.3 and 5.4). The earliest changes are seen in the papillary dermis, where there is striking dilatation and tortuosity of the superficial capillary loop, which is surrounded by polymorphonuclear leucocytes and a lesser number of mononuclear cells. The former migrate through the prickle cell layer into the parakeratotic stratum corneum to form microabscesses (of Monro), whereas the mononuclear cells move into the lower layers of the epidermis. Vesiculation owing to spongiosis of the superficial epithelium is a characteristic feature of psoriasis. Monocytochemotaxis is high in active psoriasis vulgaris, whereas polymorphonucleocytes predominate in pustular psoriasis, where a massive infiltration of the epidermis produces visible pustules. The epithelium shows marked acanthosis (hyperplasia) such that the entire epidermis within the plaque is thrown into folds and the epidermal ridges are elongated, clubbed and fused at their lower borders. Typically, the epithelium is hyperactive, and suprabasal mitotic figures are frequently evident. Studies of cell transit through the epidermis confirm this epithelial hyperproliferation and indicate that cell replacement occurs roughly seven times faster than normal. Thus the psoriatic basal cell is shed in about 4 days, whereas a normal cell is shed in about 28 days. The 'normal' skin in the psoriatic patient is also mitotically active, but not to the same degree. Originally, it was believed that the cell cycle time was shorter in psoriasis, but now it appears that there is an increased recruitment of cycling cells from the resting fraction of the basal cells of the epidermis. The scales that are shed so freely and constitute such an embarrassment in psoriasis are a direct result of the overactivity of the epithelium. The erythema of the skin is a result of the dilatation and proliferation of the capillaries in the papillary dermis.

Fig. 5.3 Psoriatic plaque. Low-power view showing hyperkeratosis with parakeratosis overlying a grossly acanthotic epidermis. The epidermal ridges are elongated, clubbed and fused at their lower borders.

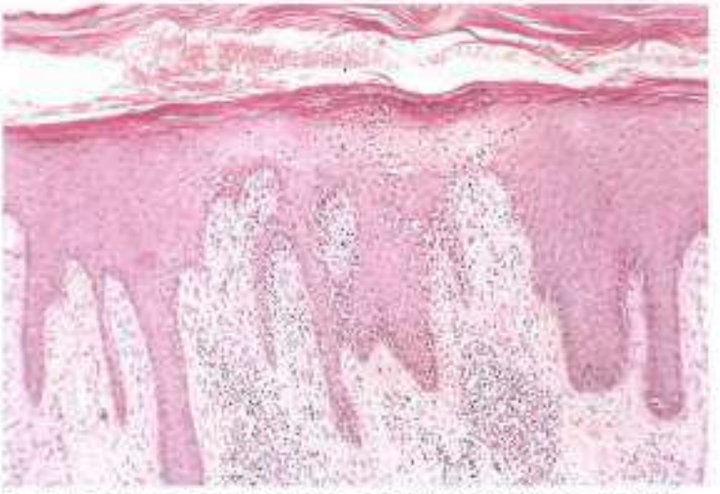


Fig. 5.4 Psoriatic plaque. The epidermis is thickened and hyperkeratotic and the epidermal ridges are elongated and fused. There is a dermal and epidermal infiltrate and dilated capillaries.

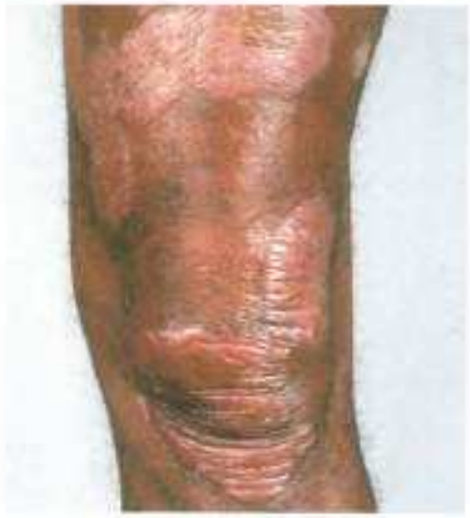


Fig. 5.5 Psoriasis vulgaris. The lesions are very well defined and a deep-red colour, even in pigmented races. The scale may not always be obvious.

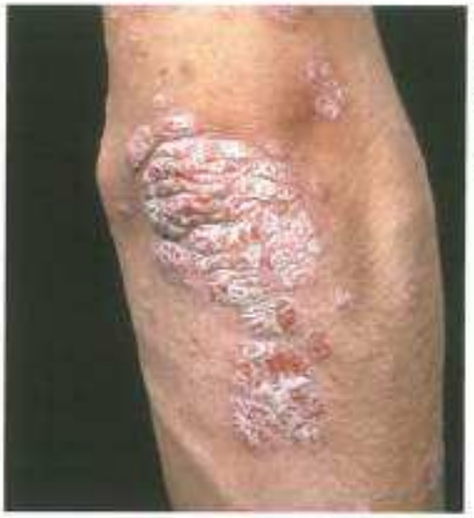


Fig. 5.6 Psoriasis vulgaris. Chronic plaques are covered by a thick silvery scale. The points of the elbows are characteristically involved and difficult to treat.

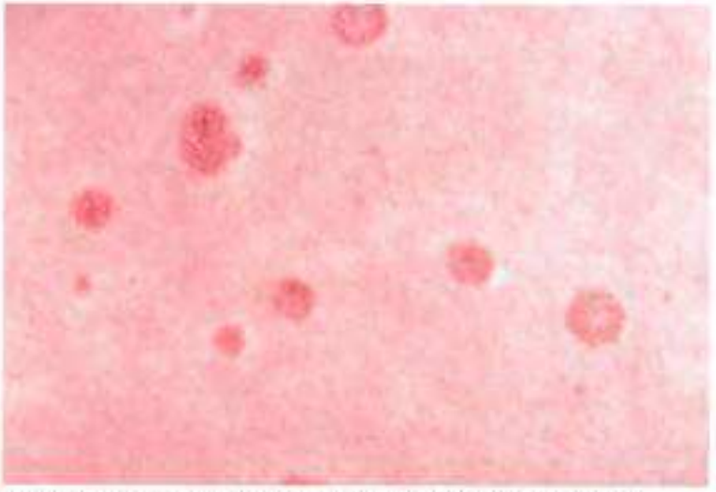


Fig. 5.7 Woronoff's ring. A clear pale halo is present around the psoriatic plaques. The significance of this phenomenon is not known.

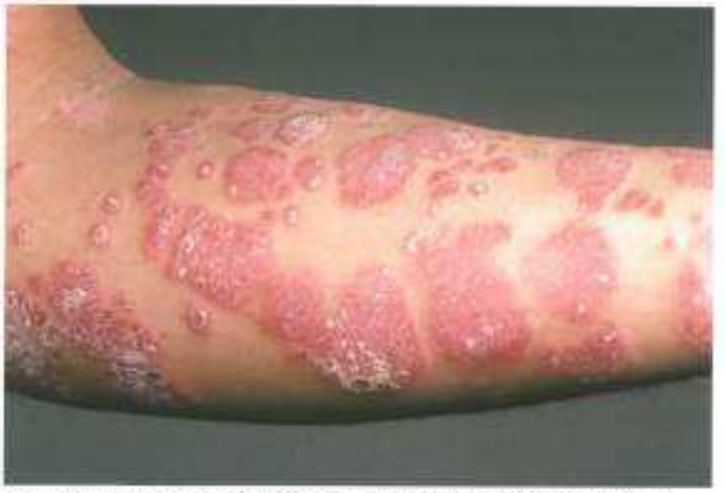


Fig. 5.8 Psoriasis. The limbs are usually affected. The lesions are very clearly delineated, are a deep-red colour and have a silvery scale. The plaques are of different shapes and sizes.

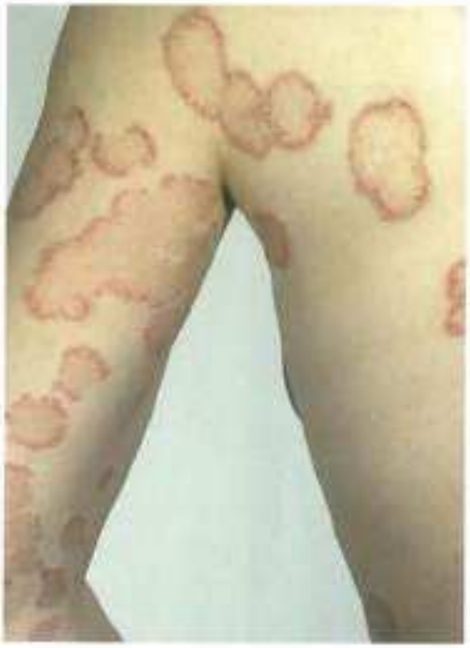


Fig. 5.9 Annular psoriasis. Healing takes place centrally in psoriasis; as a result, ring-shaped configurations may result.

Psoriasis vulgaris

Clinical Features

Symptoms

Apart from its appearance, although it may itch it is normally asymptomatic.

Morphology

The lesions are symmetrical, very well defined and slightly raised (Fig. 5.5). They are deep red in colour and have a thick white or silvery scale (Fig. 5.6), which reveals tiny bleeding points from the dilated superficial capillaries (Auspitz sign) when the suprapapillary epithelium is scraped away (grattinage). There is occasionally a clear peripheral halo or ring (of Woronoff) around the plaques (Fig. 5.7). The size and shape of the plaques vary enormously (Fig. 5.8): small plaques may coalesce into large ones. Healing takes place centrally; as a consequence, annular configurations result (Fig. 5.9).

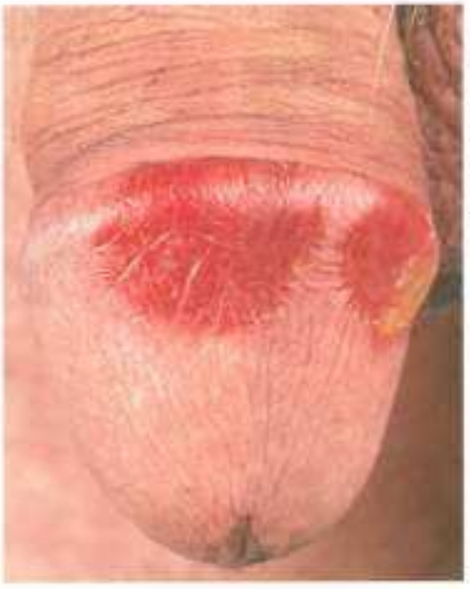


Fig. 5.10 Genital psoriasis. The plaques are very well defined and a deep-red colour. There may be no psoriasis elsewhere, although the scalp should be examined. Potent topical steroids may be used.

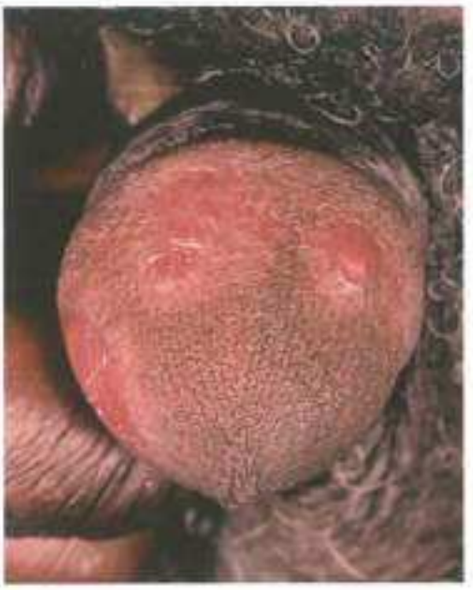


Fig. 5.11 Genital psoriasis. Well-defined, red plaques are present in this West Indian, with a minor degree of white scaling. Psoriasis is rare in black skins unless there is Anglo-Saxon ancestry.

Distribution

The sites most commonly affected are the scalp and extensor surfaces of the elbows, knees, sacrum and the limbs, but psoriasis may occur anywhere on the skin, including the genitalia (Figs 5.10 and 5.11). It is fortunately unusual on exposed areas (Fig. 5.12).

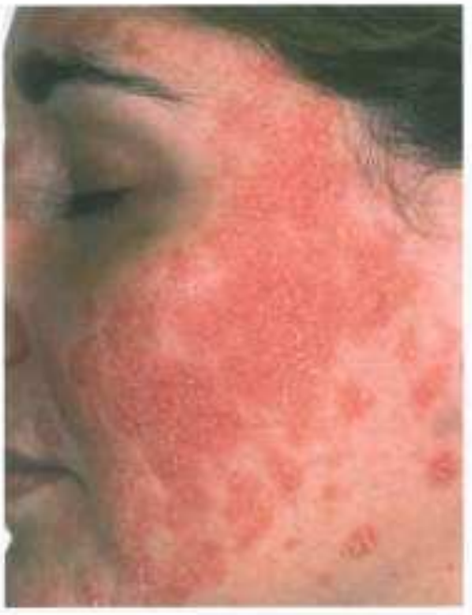


Fig. 5.12 Psoriasis. Fortunately psoriasis is uncommon on the exposed sites such as the face and backs of the hands. This degree of involvement would merit ultraviolet (if not precipitated by sunburn) or systemic therapy.

Subacute and acute psoriasis

Clinical Features

Symptoms

The area is sore and inflamed.

Morphology

The plaques are bright red (Fig. 5.13), have little surface scale and are tender to touch, unlike those in chronic psoriasis (Fig. 5.14).

Distribution

Usually extensive, and often acral and flexural.

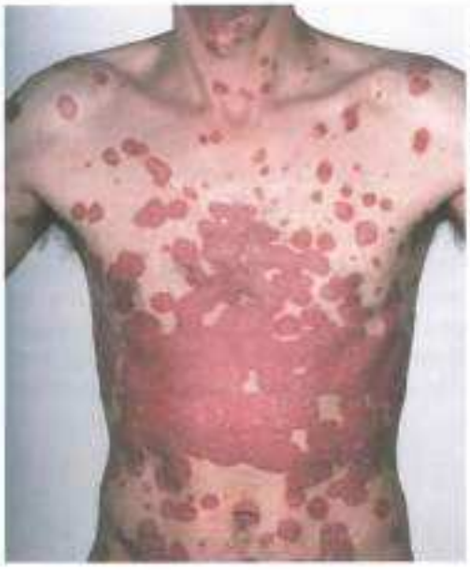


Fig. 5.13 Subacute psoriasis. In contrast to chronic psoriasis (Fig. 5.14), the plaques have no obvious scale, are a fiery red colour and sore. There is usually a provocative factor, in this case alcohol misuse.

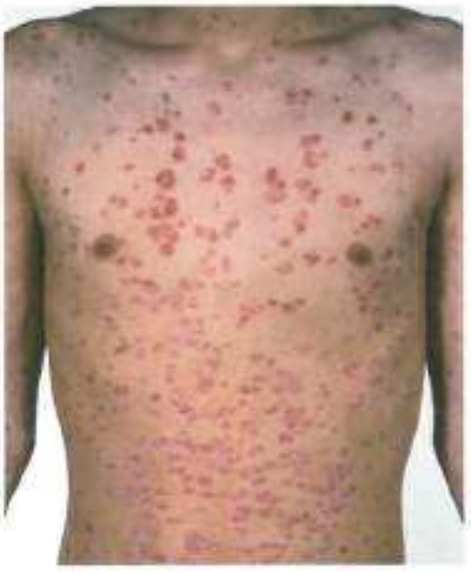


Fig. 5.14 Chronic psoriasis. The individual plaques are well defined and have a discernible thick white scale. Psoriasis may occur anywhere on the skin and be extensive.

Erythrodermic psoriasis

Clinical Features

Symptoms

Patients are red all over, unwell with a fever and leucocytosis, feel cold and shivery and cover themselves with blankets to keep warm.

Morphology

The psoriasis is a deep-red colour (erythrodermic) (Fig. 5.15) and may be scaly (exfoliative). The redness results from capillary proliferation. The scale may be thick and white, unlike in other forms of erythroderma.

Distribution

The term erythroderma implies that virtually the whole cutaneous surface is involved (Figs 5.16 and 5.17). (Psoriasis is one of the most common causes, but eczema, mycosis fungoides, Sézary syndrome, pityriasis rubra pilaris and drug eruptions may also result in erythroderma.) Temporary loss of hair and disturbance in nail growth (horizontal ridging and occasionally shedding) may occur.

Metabolic consequences of erythroderma

- **Thermoregulation** Generalized vasodilatation leads to excessive loss of body heat, central hypothermia and compensatory heat production, which ultimately causes tissue catabolism and muscle wasting. Paradoxically in the tropics, hyperthermia may occur because there is reduced sweating owing to intraepidermal occlusion of the sweat ducts in erythrodermic skin.
- **Haemodynamics** The increased cutaneous blood flow induces a high cardiac output and may lead to heart failure, particularly in those with a myocardium already compromised by hypertensive, valvular or ischaemic heart disease or by anaemia.
- **Dermatogenic enteropathy** Malabsorption with protein loss may occur, which reverts to normal with treatment of the erythroderma.
- **Impaired barrier function of the skin** Because the epidermal barrier is impaired, there is increased percutaneous water loss. Decreased urinary output and dehydration occurs if water replacement is inadequate. Increased epidermal permeability also means that care has to be taken with topical applications, particularly steroids, because systemic absorption is likely to be high. Finally, protein and iron are lost through the exfoliating scales, which may lead to hypoproteinaemia and iron deficiency anaemia.

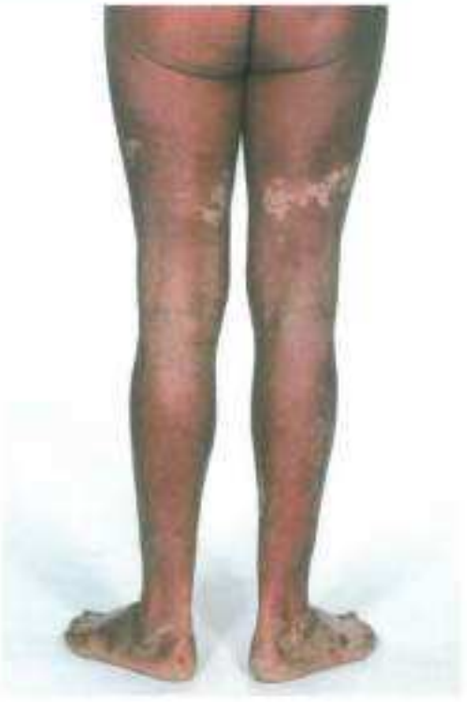


Fig. 5.15 Erythrodermic psoriasis. There is diffuse involvement of the skin. It is a deep red colour. The usual silver scaling is virtually absent. The patient was intoxicated even whilst in hospital.

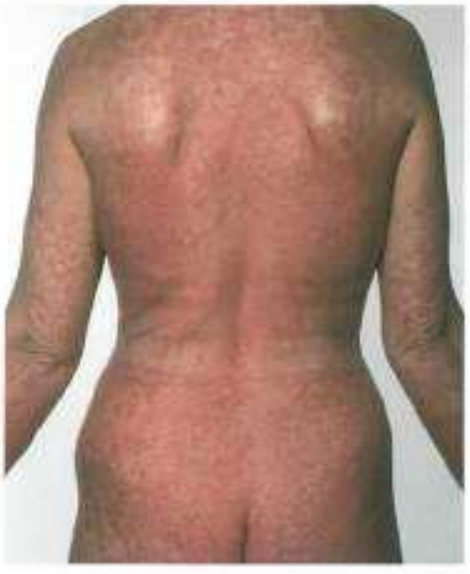


Fig. 5.16 Erythrodermic psoriasis. The skin becomes universally involved. In some areas it is red (erythrodermic) and in others scaling (exfoliating).

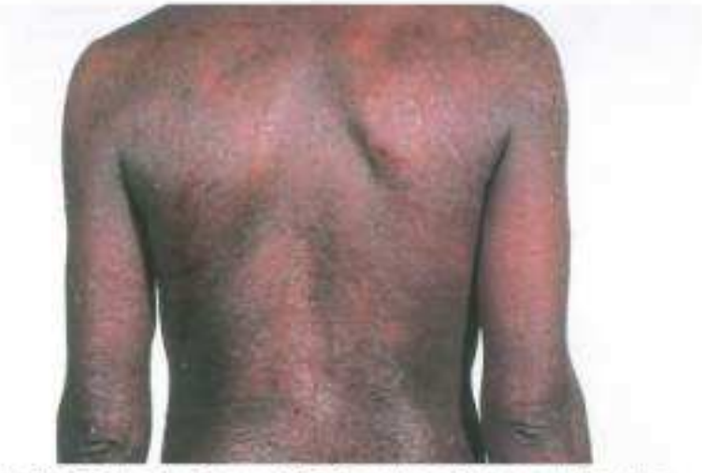


Fig. 5.17 Erythrodermic psoriasis. The erythema is less easy to discern in a brown skin but there is universal involvement and silver scales are evident.

Pustular psoriasis of the palms and soles

Aetiology

There is disagreement as to whether pustular psoriasis of the palms and soles is related to psoriasis or not. Sometimes psoriasis is found elsewhere and there is a family history, but not always, and there is no predominant HLA locus associated with it. It is also more common in females, does not improve in the summer and has a later age of onset. It is associated with diabetes mellitus, thyroid disease, smoking and various forms of arthropathy, including a specific entity known as the Sapho syndrome (synovitis, acne pustulosis, hyperostosis and osteitis). An acute form of palmo-plantar pustulosis, which may be a distinct entity, has been described under the term *pustular bacterid* (Fig. 5.18). This is an acute monomorphic outbreak of sterile pustules thought possibly to be triggered by a remote bacterial infection. There are two common forms of localized pustular psoriasis: palmo-plantar pustulosis and acrodermatitis continua of Hallopeau.

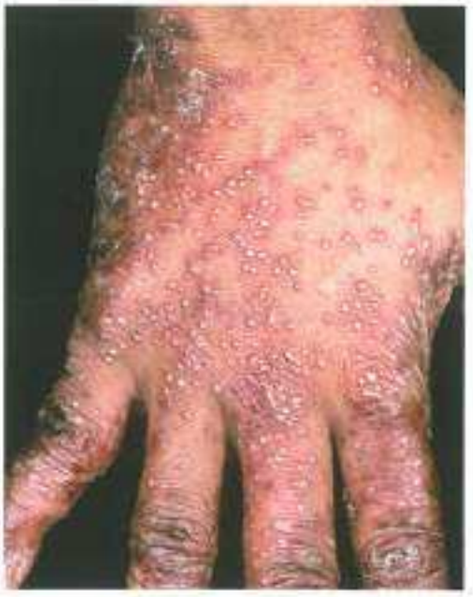


Fig. 5.18 Pustular bacterid. This is an acute monomorphic outbreak of sterile pustules precipitated in this patient by alcohol misuse; it resolved on abstention and with normalization of liver function. It may be a distinct entity or an acute variant of palmo-plantar pustulosis.

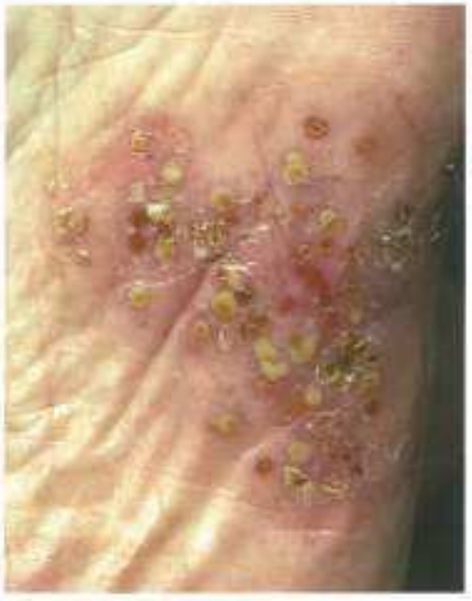


Fig. 5.19 Palmo-plantar pustular psoriasis. Sterile yellow pustules, which become brown, occur on a well-defined background of erythema on the palms or soles.

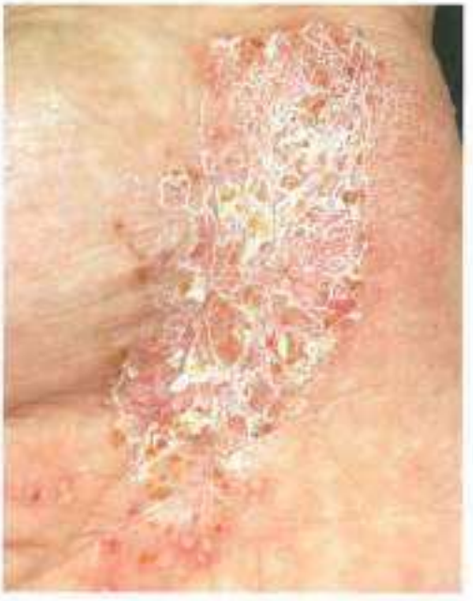


Fig. 5.20 Palmo-plantar pustular psoriasis. This is characterized by yellow pustules, which become brown, on a background of well-defined scaling and erythema.

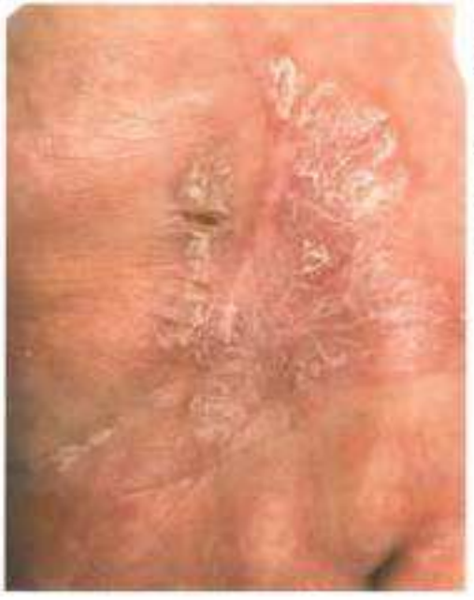


Fig. 5.21 Psoriasis of the palms. Psoriasis should be differentiated from eczema because the management is different. It usually does not itch. There are no vesicles and it is red, fissured, better defined and has a thicker scale.

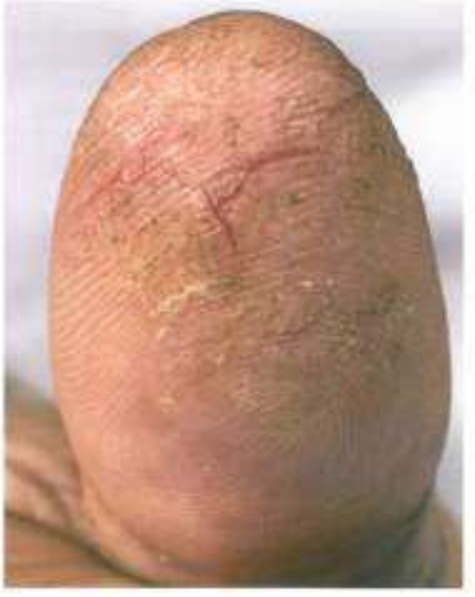


Fig. 5.22 Digital psoriasis. Psoriasis of the tips of the fingers and thumbs is dry, pink, fissured and uncomfortable. There are no vesicles, which serves to distinguish it from eczema. Topical agents are not very effective and systemic agents may be required.

PALMO-PLANTAR PUSTULOSIS

Clinical Features

Symptoms

Patients often remark on the yellow spots.

Morphology

This is characterized by yellow pustules that turn brown, on a well-defined background of erythema (Fig. 5.19) or of a psoriatic plaque (Fig. 5.20). Pustules are absent in psoriasis vulgaris (Figs 5.21, 5.22, 5.23 and 5.24).

Distribution

The plaques may be unilateral or remarkably symmetrical. They are to be found on the thenar and hypothenar eminences, and on the central and distal parts of the palms and soles.

ACRODERMATITIS CONTINUA OF HALLOPEAU

Symptoms

An unsightly rash of the digit with involvement of the nail.

Morphology

This condition typically consists of sterile pustules.

Distribution

It affects the tips of the fingers (Fig. 5.25) and, less commonly, the toes. Only one digit may be involved and may lead to nail dystrophy (Fig. 5.26). It is almost always mistaken for a paronychia, but the pustules are sterile. The condition may gradually spread to other digits. Unlike palmo-plantar pustulosis, this does occur sometimes in children, but usually it begins quite late in life. It is more common in females and there is a definite risk of progression to generalized pustular psoriasis.

Fig. 5.23 Psoriasis. Psoriasis vulgaris may be distinguished from pustular psoriasis of the palms and soles by the absence of pustules. The latter is positively associated with cigarette smoking.

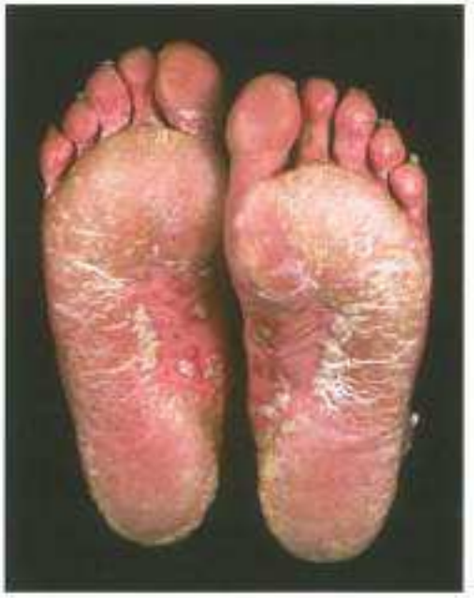


Fig. 5.24 Psoriasis. The lesions tend to be symmetrical, well-defined, red and have a thick scale. They may be fissured and painful in cold weather. Pustules may be present.

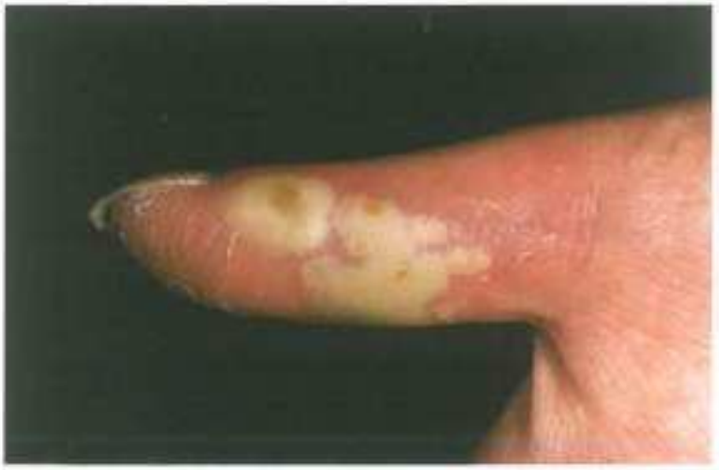


Fig. 5.25 Acrodermatitis continua of Hallopeau. Sterile pustules affect the tips of one or more digits. It occurs in childhood or late adult life and may progress to generalized pustular psoriasis.

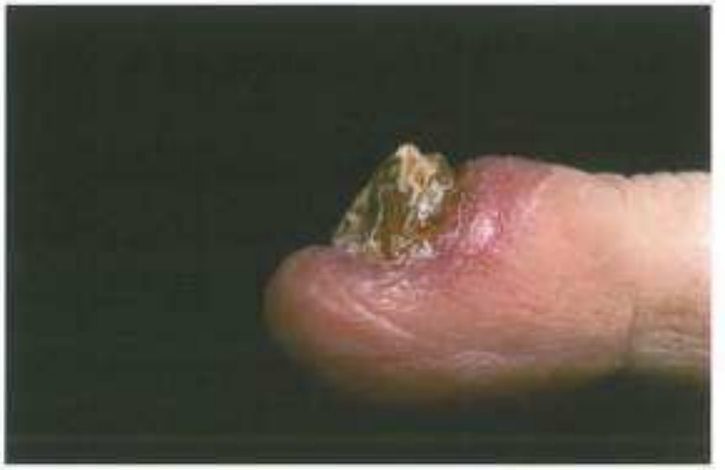


Fig. 5.26 Acrodermatitis of Hallopeau. This is a localized pustular psoriasis that involves the periungual skin and produces nail dystrophy.

Generalized pustular psoriasis

This is a severe acute generalized pustular form of psoriasis described by von Zumbusch associated with fever, arthropathy and leucocytosis.

Aetiology

This is an extreme form in which all the main pathological features of psoriasis are accentuated. There is lymphocytic infiltration initially, with intense papillary and epidermal oedema, resulting in spongiosis. Masses of neutrophils form the so-called spongiform pustules of Kogoj, and these abscesses are visible macroscopically. There is acanthosis, with elongation of the rete ridges and parakeratotic stratum corneum. Provoking factors are usually identifiable and include progression from acrodermatitis continua of Hallopeau. There may be a prior family history of psoriasis.

There is a strong association with HLA-B27, which probably explains the frequent association of generalized pustular psoriasis with arthritis.

It very rarely occurs in pregnancy (see Ch. 28).

Clinical Features

Symptoms

The patient feels ill, is feverish and uncomfortable (the lesions may burn).

Morphology

Extensive sheets of tiny, sterile, yellow pustules (Fig. 5.27) cover the skin, which is fiery red and sore (Fig. 5.28). The pustules occur in waves and exfoliate as they dry (Figs 5.29 and 5.30). They may occur in various configurations – as isolated pustules, lakes of pus, in circinate configurations or with plaques of erythema with a collarette of pustules at the margins – usually on a background of generalized erythroderma.

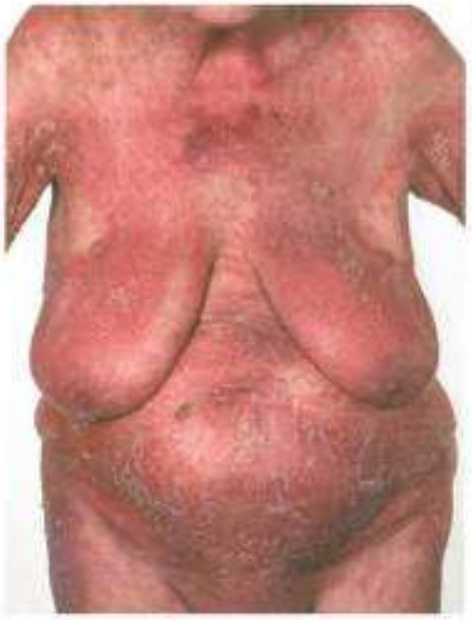


Fig. 5.27 Generalized pustular psoriasis. Extensive sheets of tiny sterile pustules cover the skin, which is bright red and sore.

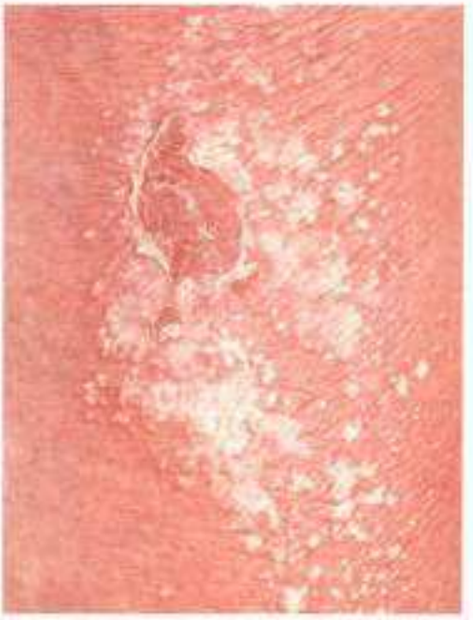


Fig. 5.28 Generalized pustular psoriasis. The pustules occur in waves and peel (exfoliate) as they dry.

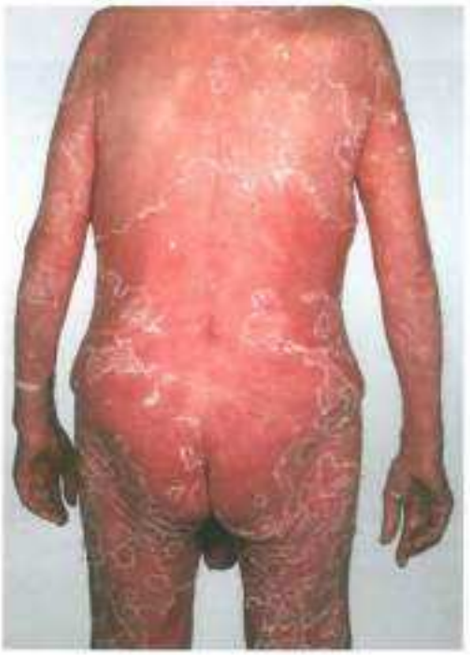


Fig. 5.29 Generalized pustular psoriasis. The patient is erythrodermic. As the pustules dry, there is exfoliation, often in circinate configurations.

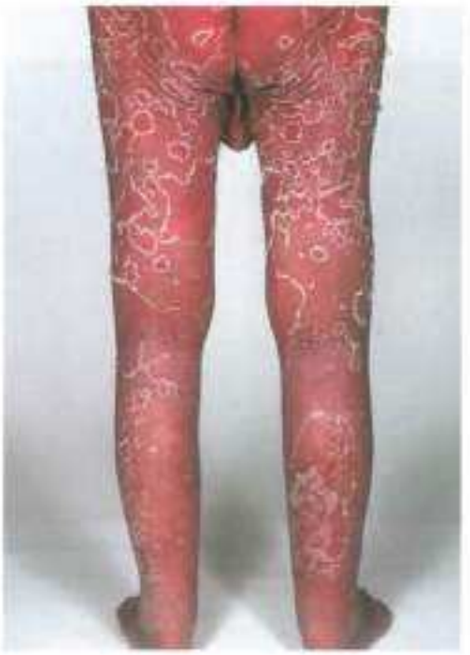


Fig. 5.30 Generalized pustular psoriasis. This patient had psoriasis, which cleared with ciclosporin given to prevent organ rejection following a renal transplant. As the dose was reduced, the psoriasis returned in a pustular form.

Distribution

Any area of the body may be involved, particularly the flexures and genital regions. The nails may become thickened or separated by subungual lakes of pus. Hair loss is very common, often quite marked within a few days, although sometimes the telogen effluvium variety occurs in less severe disease. The buccal mucosa and tongue may be involved, having a geographical appearance. An inflammatory arthritis is not unusual.

Systemic Features

This condition is serious and it did have an appreciable mortality. Initially there is an absolute lymphopenia, but this is followed by a leucocytosis with increased numbers of polymorphs. The erythrocyte sedimentation rate (ESR) is raised. Serum albumin concentrations are reduced (often profoundly), as are those of calcium and zinc. The patient may become oligaemic and there is a danger of acute renal tubular necrosis. Liver damage may occur (leading to jaundice) secondary to the oligaemia, general toxicity or, occasionally, owing to a drug reaction. Congestive cardiac failure, venous thrombosis and pulmonary embolism are not uncommon. Secondary skin sepsis and septicaemia may occur.

Differential Diagnosis

The diagnosis is not difficult, but a drug-induced eruption (Figs 5.31 and 5.32) simulating pustular psoriasis (*acute generalized exanthematic pustulosis*) has been described with β-lactam antibiotics, macrolides, penicillin and others (Ch. 18). Pustular psoriasis may occur in pregnancy (Figs 5.33 and 5.34 (Ch. 28)).

Fig. 5.31 Acute generalized exanthematic pustulosis. An exanthematic pustular dermatosis simulating pustular psoriasis occurs secondary to various drugs, including antibiotics. It is transient and the pathology is of a vasculitis.

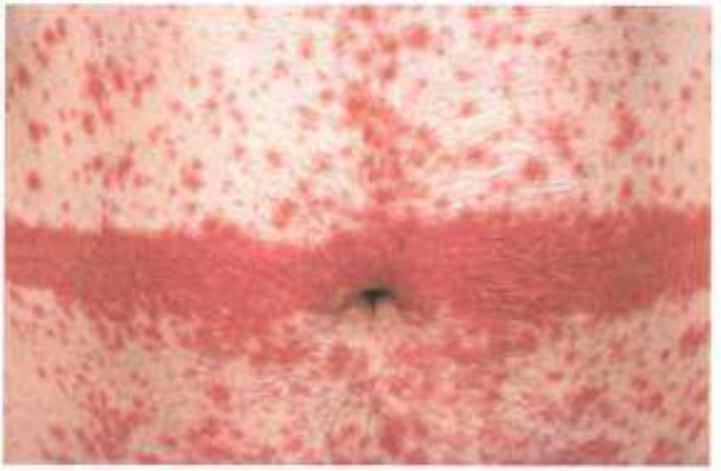


Fig. 5.32 Acute generalized exanthematic pustulosis (AGEP). This is a toxic pustuloderma which simulates generalized pustular psoriasis but is associated with a drug hypersensitivity. A marked Koebner phenomenon is present.

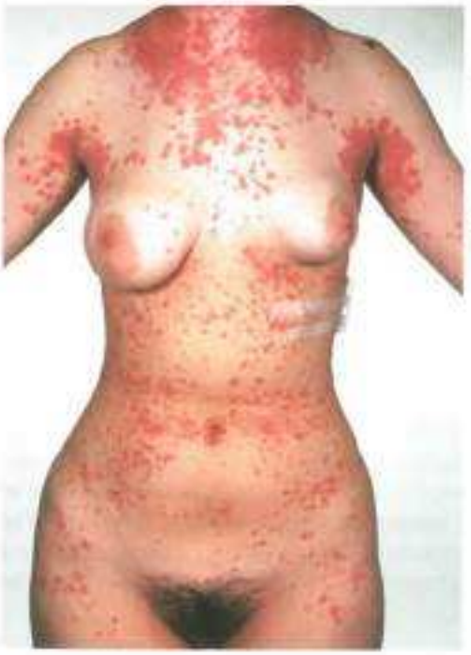


Fig. 5.33 Pustular psoriasis of pregnancy. There is a tendency for flexural involvement. It is a serious disorder with a high risk of fetal abnormalities. She was 16 weeks pregnant here and subsequently lost her child.

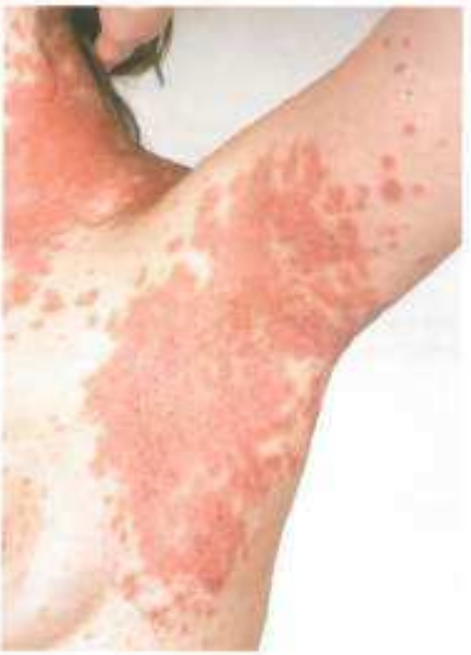


Fig. 5.34 Pustular psoriasis of pregnancy. There is a tendency for flexural involvement. It is a serious disorder with a high risk of fetal abnormalities.

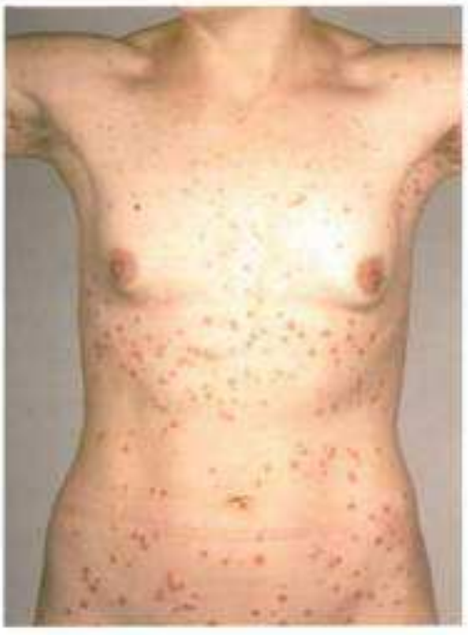


Fig. 5.35 Guttate psoriasis. Small droplike (guttate) red scaly papules occur on the trunk and limbs after a streptococcal throat infection.

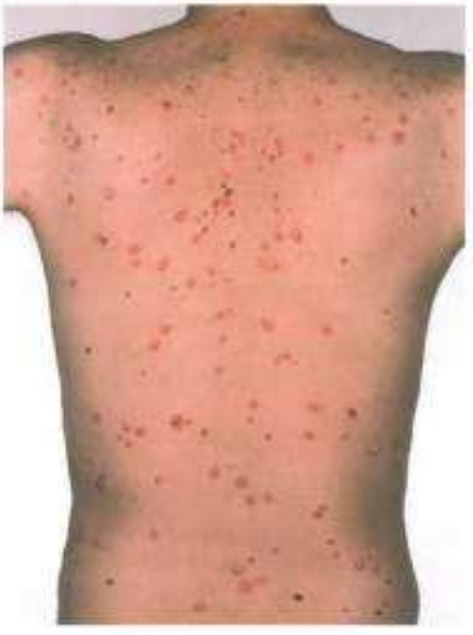


Fig. 5.36 Guttate psoriasis. The lesions are well-defined, small red scaly papules. It occurs explosively 3–4 weeks after a throat infection, despite appropriate antibiotic therapy. It persists for 3 months.

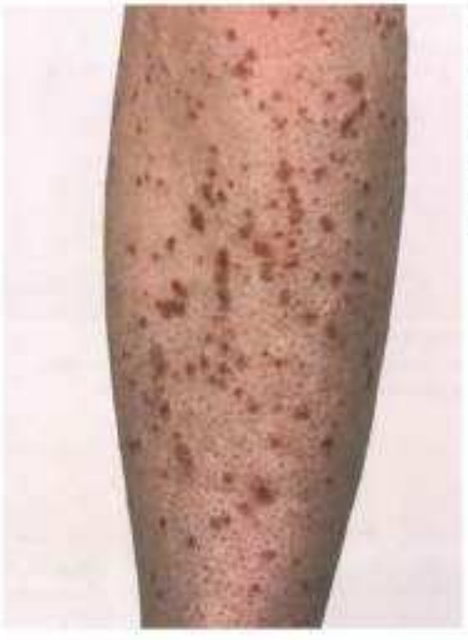


Fig. 5.37 Guttate psoriasis. The papules are very small, like a 'drop' (Latin: gutta) of psoriasis on the skin. The basic characteristics of psoriasis (a well-defined, red lesion with a silver scale) are retained.

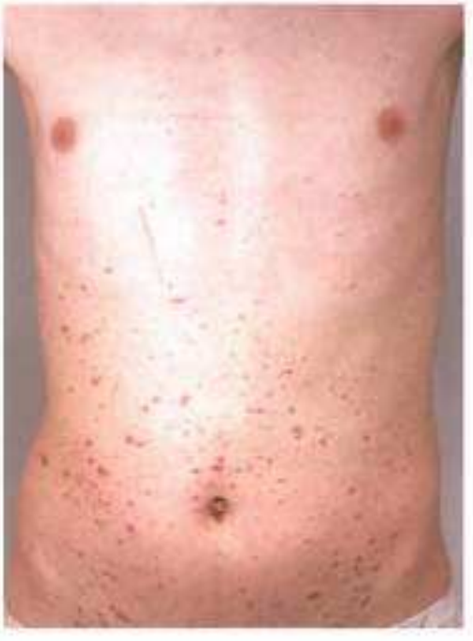


Fig. 5.38 Guttate psoriasis.
The onset is explosive with a myriad of small, red papules with a thick, white scale on the torso and limbs 3 weeks after a streptococcal throat infection. Note the line of papules on the right side of his chest secondary to a scratch (Koebner phenomenon).

Guttate psoriasis

Aetiology

A common disorder of adolescence or young adults. It commences acutely 3 or 4 weeks after a severe streptococcal throat infection, despite adequate antibiotic therapy.

Clinical Features

Symptoms

An acute onset of a rash following a sore throat.

Morphology

There is an eruption of very small, droplike ('guttate') papules (Figs 5.35 and 5.36), each of which is a deep-red colour (Fig. 5.37) and often has a characteristic silver scale on its surface.

Distribution

The papules occur on the trunk (Fig. 5.38) and limbs; there is sparing of the face (usually), palms and soles.

Differential Diagnosis

The history of the sore throat, the absence of a herald patch and the more widespread distribution helps to distinguish this from pityriasis rosea. In most cases, the condition resolves completely within 4 months, and in some patients it never recurs. In others, it is either an exacerbation of a pre-existing psoriasis, which returns to its former state, or it is followed by minor patches of psoriasis.

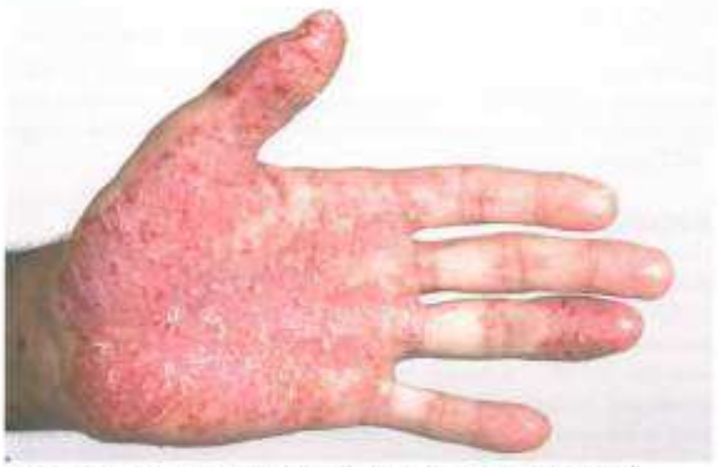


Fig. 5.39 Reiter's syndrome. Arthritis (particularly ankylosing spondylitis), conjunctivitis and psoriasiform lesions occur on the palms and soles following urethritis or dysentery. Similar changes occur with HIV.

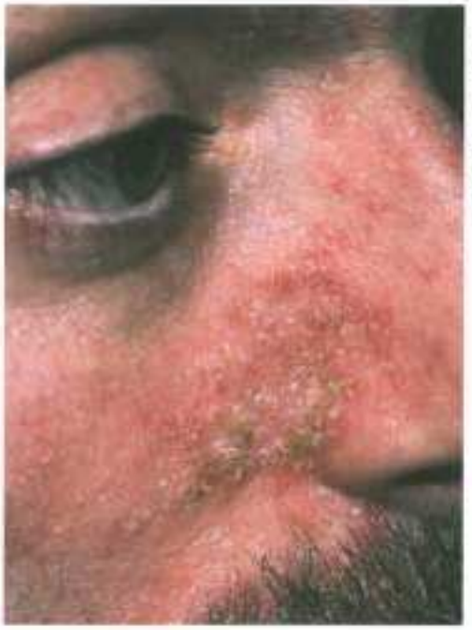


Fig. 5.40 HIV and psoriasis. Psoriasis is more common with HIV infection and the acquired immunodeficiency syndrome (AIDS) and should be suspected in resistant inflammatory eruptions on the face.

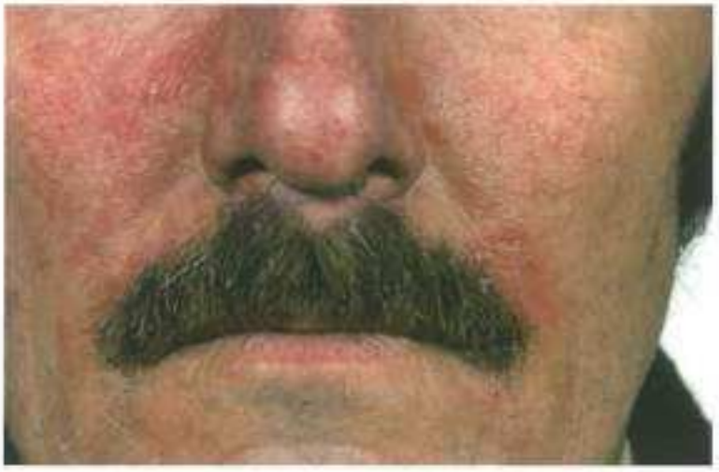


Fig. 5.41 HIV and psoriasis. Psoriasis on the face is more common with HIV infection and the acquired immunodeficiency syndrome (AIDS).

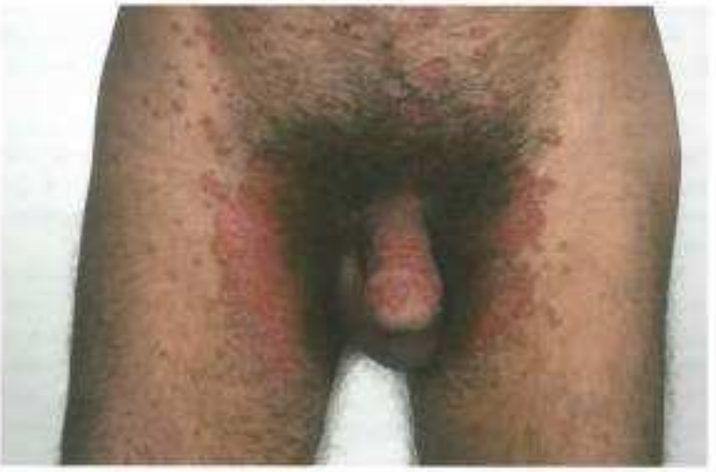


Fig. 5.42 HIV and psoriasis. Psoriasis is often more acute and sore and flexural in distribution. Systemic therapy is usually indicated.

HIV and psoriasis

Aetiology

Psoriasis in patients with HIV differs from classic psoriasis. It is more severe, responds poorly to treatment, there is usually a negative family history and there is no increase in HLA antigens except for HLA-27 in the setting of Reiter's syndrome (Fig. 5.39) and in patients with asymmetrical polyarthritis. It is three times more common.

Clinical Features

Symptoms

The rash may be sore, itchy and extensive.

Morphology

The plaques are often red, raw and subacute.

Distribution

It particularly involves the face, often in a seborrhoeic distribution (Figs 5.40 and 5.41), flexures (Fig. 5.42) and extremities, including the nails (Fig. 5.43) ('inverse psoriasis').

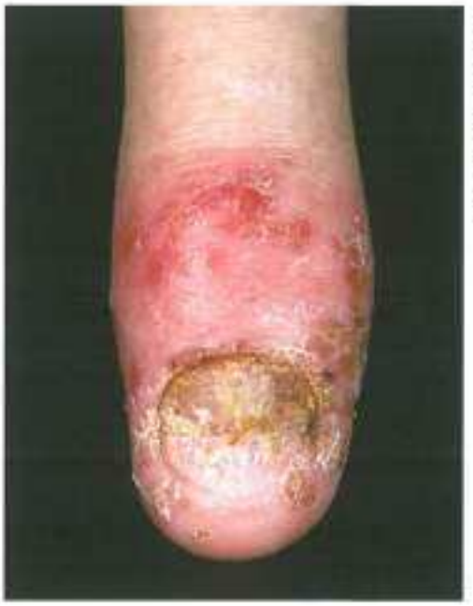


Fig. 5.43 HIV and psoriasis. The nails are dystrophic and there is periungual psoriasis and distal interphalangeal joint arthritis. This simulates Reiter's syndrome and is common in HLA-B27- and HIV-positive patients.

Management of psoriasis

Psoriasis vulgaris is comparatively easy to treat. It responds to tar, dithranol and narrowband ultraviolet light. There are often readily discernible provocative factors for subacute, acute and erythrodermic psoriasis, which should be addressed. These may be:

- inappropriate treatment
- abrupt reduction of immunosuppressive therapy
- sudden cessation of superpotent topical or systemic steroids
- drugs (including alcohol)
- infection (including HIV)
- pregnancy (and rarely pustular psoriasis)
- physical or emotional illness

Bland topical therapy and diluted topical steroids coupled with systemic agents such as retinoids (but not in pregnancy) or methotrexate. Ultraviolet light and PUVA should be used with care and are best avoided in generalized pustular psoriasis. Both the latter and erythrodermic psoriasis are associated with systemic abnormalities and toxicity, viz. hypothermia, fluid imbalance, sepsis and concomitant medical conditions and have an appreciable morbidity and, in the past, significant mortality. Hospitalization, systemic agents (such as retinoids and ciclosporin) are required. Methotrexate, although effective, should be administered in much smaller doses in generalized pustular psoriasis because bone marrow toxicity is much more likely to occur with standard regimens.

Topical therapy is usually ineffective in ordinary or pustular psoriasis of the palms and soles. Hand and foot PUVA (topical or systemic) or systemic agents are generally indicated.

Guttate psoriasis is widespread and ointments are clearly impractical. Tar baths coupled with UVB therapy (the Goeckerman regimen) were used for many years but narrowband ultraviolet has superseded this and the psoriasis clears rapidly. Treatment of the streptococcal throat has little if any effect on the evolution of the psoriasis.

The management of HIV-associated psoriasis is difficult. Methotrexate and ciclosporin are relatively contraindicated becaue of their immunosuppressive effects. PUVA, although potentially immunosuppressive, is permissible but narrowband UVB is preferable. Retinoids are the first line of management. HAART (highly active antiretroviral therapy) does improve some patients but others may deteriorate. Zidovudine has been used with some success.

Reiter's syndrome

A mucocutaneous disorder occurring particularly in HLA-B27-positive young males following a venereal or enteric infection. It is associated with an asymmetrical non-suppurative polyarthritis, inflammatory eye changes and a psoriasiform eruption.

Aetiology

The arthritis is reactive, most commonly to *Chlamydia trachomatis*, but also to *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter* and *Mycoplasma* infections. Chlamydial DNA and RNA has been found in joints, raising the question as to whether it is a septic rather than reactive arthritis. It is also associated with HIV infection. It usually begins in the third decade, but may occur in children following enteritis. It occasionally occurs in an incomplete form in females who are HLA-B27 negative, in contrast to males, in whom there is a 25-fold higher HLA-B27 positivity. The histology of the rash is indistinguishable from that of ordinary psoriasis.

Clinical Features

Symptoms

An acute arthritis, conjunctivitis, fever, fatigue and a rash follows within 3 weeks of urethritis or enteritis. It is occasionally chronic and there may be weight loss.

Morphology

The lesions, which are well defined, often become quite hyperkeratotic (Fig. 5.44) or rupioid. (The latter term refers to a limpet-like, cone-shaped lesion that protrudes a centimetre or so from the skin surface.) They may coalesce, producing an appearance resembling that of a relief map. This condition is known as *keratoderma blenorrhagicum*.

Distribution

The soles are almost always involved. Psoriasiform changes, sometimes with pustules, are found around the nails and elsewhere.

Lesions appear on the penis (Fig. 5.45) in about 25% of patients. In the uncircumcised they are well demarcated, red and serpiginous, with a ragged white border. They are painless but may erode and become moist. They are often multiple. In circumcised patients, they are dry (*balanitis circinata sicca*), psoriasiform and hyperkeratotic.

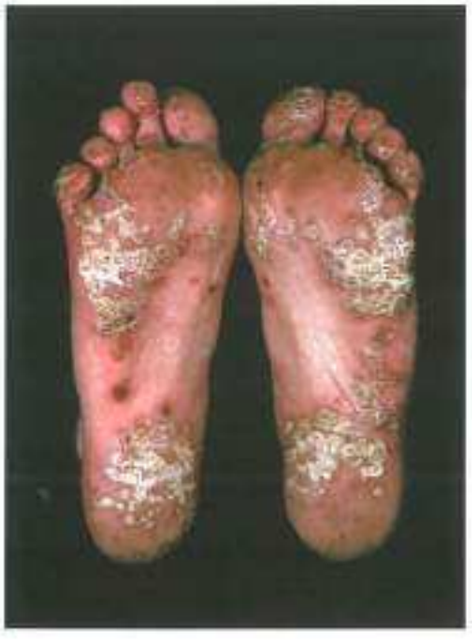


Fig. 5.44 Reiter's syndrome. The soles are almost always involved. The plaques are well defined and become quite hyperkeratotic; they may coalesce, resembling a relief map. This is known as keratoderma blenorrhagicum.

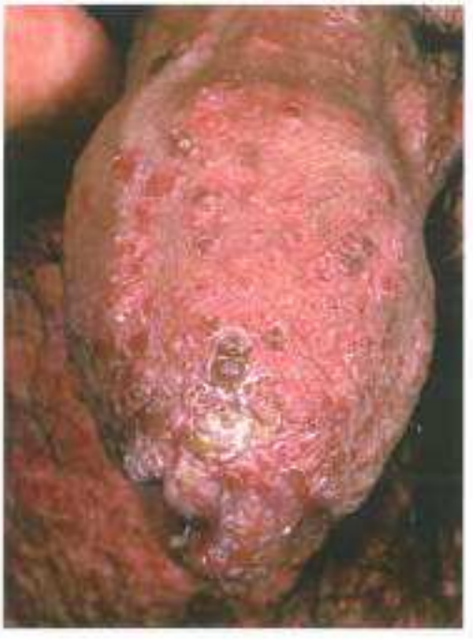


Fig. 5.45 Reiter's syndrome. The penis is often involved with a psoriasiform eruption. This is a mucocutaneous disorder associated with inflammatory eye changes and an asymmetric polyarthritis.

A minority of patients have oral lesions involving, in declining order of frequency, the palate, uvula, tongue, buccal mucosa and lips. The lesions commence as vesicles but rapidly become erosions with a surrounding erythema.

The joint and eye involvement contributes to most of the morbidity. There is an asymmetric polyarthritis affecting predominantly the knees, ankles and distal interphalangeal joints. There may be sacro-iliitis and diffuse swelling of an entire toe (sausage digit). Tendonitis, especially Achilles, calcaneal spurs and plantar fasciitis may be particularly chronic. Rheumatoid nodules do not occur. Conjunctivitis (usually bilateral with a sterile mucopurulent discharge), uveitis and keratitis constitute the eye signs.

Management

The diagnosis is a clinical one but urethral smears and stool samples should be sent for microbiology. The ESR, C-reactive protein and globulins may be raised. The joints should be X-rayed and the patient tested for HLA-B27 and HIV.

Organisms such as *Chlamydia* sp. should be treated with tetracycline-related drugs, but this may not modify the course of the disease. The joints and eyes should be managed by the respective specialists.

The penile lesions usually respond to topical corticosteroids. The other cutaneous lesions should ultimately resolve but may require systemic therapy, particularly with retinoids, methotrexate or ciclosporin. In HIV patients the former is to be preferred.

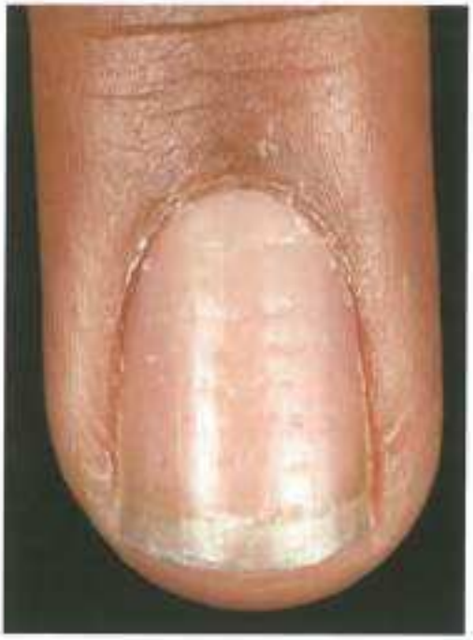


Fig. 5.46 Pitting of the nails. Tiny pits are apparent and are caused by the loss of parakeratotic areas in the nails. The changes are often symmetrical.

Psoriasis of the nails

Clinical Features

One-third of patients with psoriasis have nail changes increasing to three-quarters if they also have arthritis. The nails may be affected alone. There are four main varieties of nail change.

- **Pitting** This may occur in a scattered, random manner (Fig. 5.46) or uniformly, producing horizontal or vertical lines. The nails are generally affected symmetrically, but not always. The pits are caused by parakeratosis: these areas are weaker than the surrounding nail and fall out to form the pits.
- **Onycholysis** This is caused by separation of the nail plate from the nailbed by subungual psoriasis. It is usually symmetrical and there is often a yellow/orange discoloration between the proximal pink, healthy nail and the white/yellow, distal, separated free edge (Fig. 5.47).
- **Subungual hyperkeratosis** Severe dystrophy (Fig. 5.48) and even temporary nail loss result from more pronounced subungual psoriasis.
- **Pustular psoriasis** In pustular forms of psoriasis involving the nail-folds, more destructive changes occur, with gross hyperkeratosis and ultimately separation of the nails. This is particularly seen in the Hallopeau form.

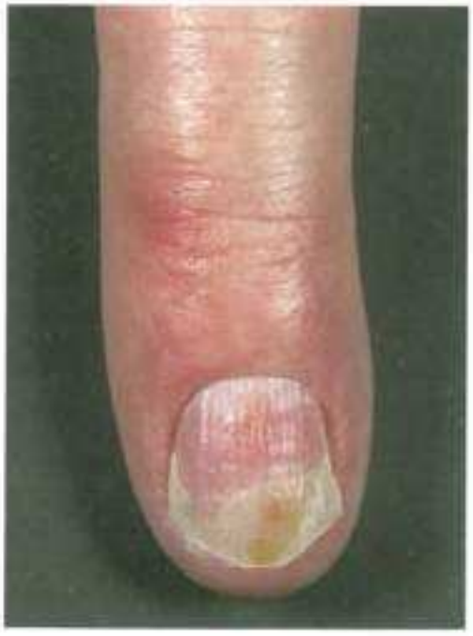


Fig. 5.47 Onycholysis. The distal nail plate is lifted away from the nailbed by psoriasis and has a creamy yellow appearance.

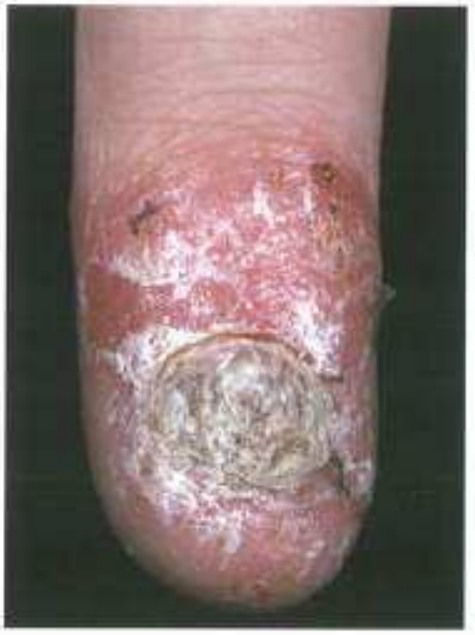


Fig. 5.48 Psoriatic onychodystrophy. Psoriasis sometimes causes a severe distortion of the nail. This may be seen with localized pustular psoriasis, HIV, Reiter's syndrome and occasionally in children, as here. Nail clippings are mandatory to exclude fungal infection.

Management

Fungal infections are important differential diagnoses because they are treatable. It is, therefore, wise to take samples for mycology as a routine. Effective local treatment is limited but spontaneous resolution may occur.

- **Steroids** A scalp application formulation may be put under the nail, or triamcinolone administered intralesionally to the nailfold via a needle or, less uncomfortably, a dermojet. There may be some improvement but it usually relapses.
- **Systemic therapy** All forms of systemic therapy will improve the nails, but such treatment for the nails alone must be balanced against potential side-effects.

Psoriatic arthropathy

Aetiology

Although psoriasis and arthritis are associated, clinical, genetic and immunological studies do not correlate well. In 15% of patients, the joint and skin changes are simultaneous in onset. In 60%, the psoriasis precedes the joint changes, and in 25% joint disease precedes the skin changes by up to a decade or more. Arthritis can occur without skin changes and, clearly, vice versa. There seems to be no relationship between the severity of the skin changes and the joint activity. Psoriasis is associated with HLA-Cw6, but this antigen is not obviously linked with arthritis unless there is coexisting psoriasis. There is, however, a definite association between HLA-B27 and radiological evidence of sacroiliitis, and a strong association of HLA-B27 with generalized pustular psoriasis and erythrodermic psoriasis. It is probable that psoriasis and psoriatic arthropathy are associated with different susceptibility genes.

Psoriasis is associated with a T cell infiltration of the skin and there are increased lymphokines originating from T helper type 1 cells, with increased levels of IL-2 and IFN-γ; by comparison, in arthritis IL-2 and IFN-γ levels are low. Also, if $CD4^+$ T lymphocytes derived from psoriatic skin are injected into severe combined immunodeficient mice, they can transform previously transplanted normal human skin in these animals into psoriatic skin, but none of the animals develops arthritis, suggesting that the skin and joint diseases are not mediated by the same cells (or that mice joints respond differently to those of humans).

Clinical Features

There are at least five different types of psoriatic arthropathy. The most important ones are:

- **Asymmetrical arthritis** This usually involves a small number of joints. There are few erosions, good preservation of function and infrequent deformity.
- **Symmetrical polyarthritis** This is frequently erosive, deforming and disabling (Fig. 5.49) but can be distinguished from rheumatoid arthritis because the distal interphalangeal joints are particularly involved, as opposed to the proximal ones. There is often spondylitis and the rheumatoid factor is negative.
- **Ankylosing spondylitis with or without peripheral arthritis** The spondylitis of the spine is similar to that of ankylosing spondylitis and a peripheral arthritis may occur. Other joints that may be involved are the cervical, spinal, temporomandibular and sternal joints. The rheumatoid-type nodules do not occur and tendon sheath effusions are uncommon. Inflammatory eye changes are, however, not unusual.

Management

Non-steroidal anti-inflammatory drugs, gold, penicillamine, methotrexate and azathioprine are standard treatments. Biologics are increasingly being used.

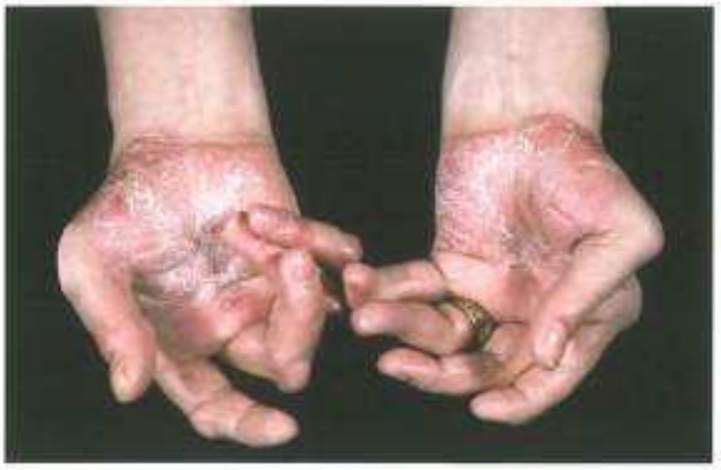


Fig. 5.49 Psoriatic arthritis. Both psoriasis and a deforming symmetrical polyarthritis are present. The distal interphalangeal joints are involved and not the proximal ones; the rheumatoid factor is negative (unlike in rheumatoid arthritis).

Drug therapies for psoriasis

Although usually chronic, psoriasis is a dynamic disease, waxing and waning in intensity throughout life. It is not sufficient simply to make a diagnosis of psoriasis; as with any other chronic disease with a limited number of therapeutic options, it calls for considerable skill in management. Fortunately, it is not usually visible (Fig. 5.50), but it causes untold suffering (Fig. 5.51). It is important to take a good history: this may reveal the cause of the outbreak (Fig. 5.52). This and an assessment of the body surface area, erythema, scaling and induration known as the PASI (psoriasis area and severity index) will influence the decision as to what agents to use and, in particular, when to use systemic drugs.

Topical Therapy

Tar

Tar is a complex mixture derived from coal. It smells and is messy, but it is effective in psoriasis although its mode of action is unknown. It may be combined with UV light, salicylic acid or topical steroids.

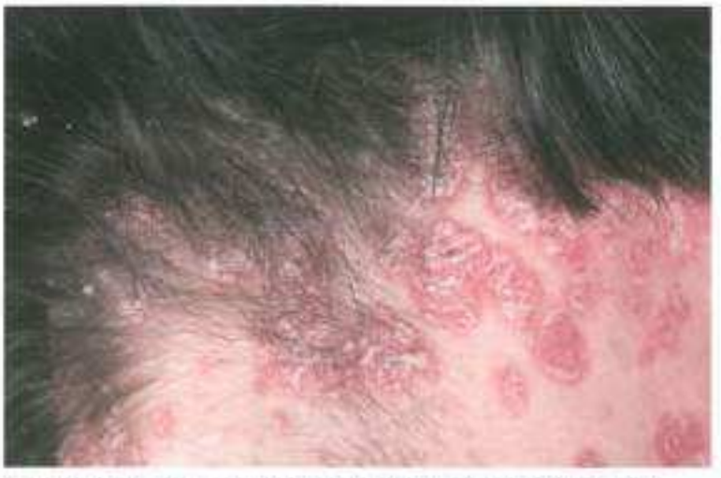


Fig. 5.50 Alcohol misuse and psoriasis. Alcohol makes psoriasis worse. Clinically, psoriasis is more acute and favours the face, extremities and flexures, rather like in HIV infection but unlike psoriasis vulgaris.

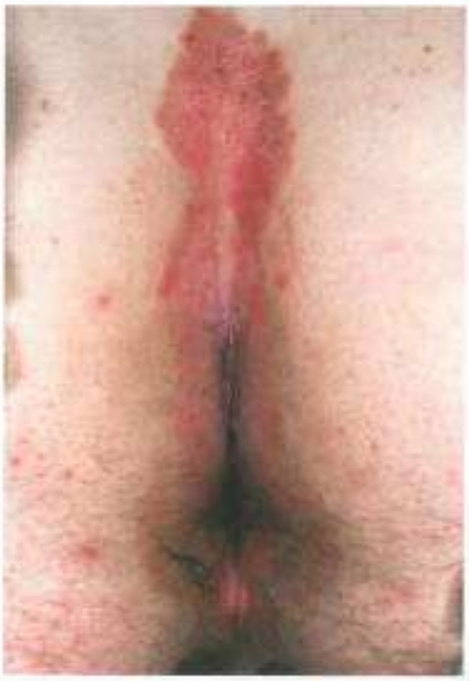


Fig. 5.51 Psoriasis. Psoriasis is symmetrical, well defined and a deep red colour. It may be sore in the perianal or genital regions and deeply embarrassing.

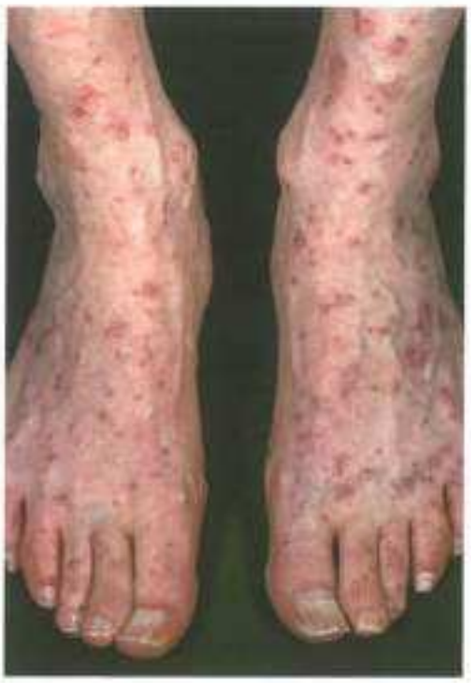


Fig. 5.52 Oxyprenolol psoriatic drug eruption. The cause of a psoriasiform rash may be a drug. This rash had features of psoriasis, lichen planus and eczema but fitted none of these diagnoses exactly and was caused by a β-blocker.

- **With UV light** Tar is a photosensitizer. Goeckerman popularized a treatment with tar baths followed by exposure to UVB, which is particularly indicated for guttate psoriasis and psoriasis vulgaris.
- **With salicylic acid** Salicylic acid is a keratolytic. It removes the psoriatic scales and improves the penetration of medicaments combined with it. Coal tar and salicylic acid ointment is suitable for chronic plaque psoriasis. Ung. cocois co. (60% coconut oil, 13% emulsifying wax, 12% coal tar solution, 9% yellow soft paraffin, 4% precipitated sulphur, 2% salicylic acid), or cocois is helpful for scalp psoriasis. It should be applied at night, covered with a scarf or bath hat, and washed out the next day with a tar shampoo. Dithranol can be added to the ung. cocois co., starting at 0.1% concentration (although not in white-haired individuals, because it stains). Applications by a skilled practice nurse can make all the difference.
- **With steroids** Tar occasionally irritates the skin and causes a folliculitis. Combination with hydrocortisone can prevent this.

Tar is a carcinogen in experimental animals and also in workers who are continually exposed to it, but there is no good evidence to suggest that it has this effect in psoriasis.

Glucocorticosteroids

Potent and very potent steroids do have an effect in psoriasis. However, usually only the scale is removed and the disease tends to relapse quickly when they are withdrawn. Many say that topical steroids should be avoided, particularly because misuse and side-effects are common (Figs 5.53 and 5.54). However, this is a counsel of perfection, as steroids are cosmetically acceptable and easy to use, whereas tar and dithranol require time and patience. Steroids are indicated for the patient with

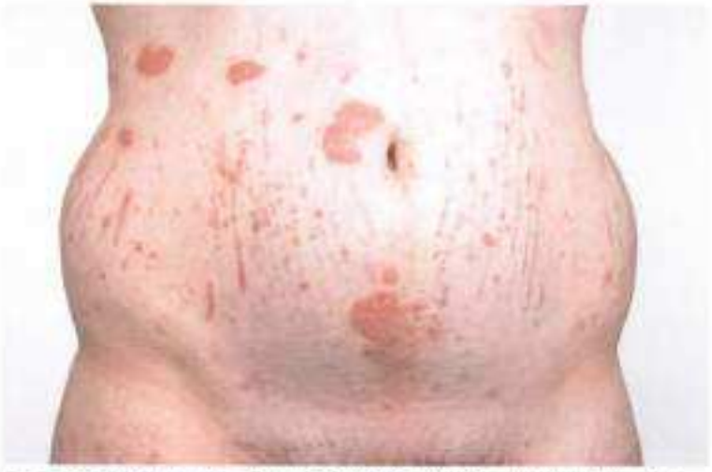


Fig. 5.53 Topical steroid misuse. Superpotent steroids are unsatisfactory for widespread psoriasis. Atrophy, purpura, striae (illustrated here) and Cushing's syndrome may result and the psoriasis returns.

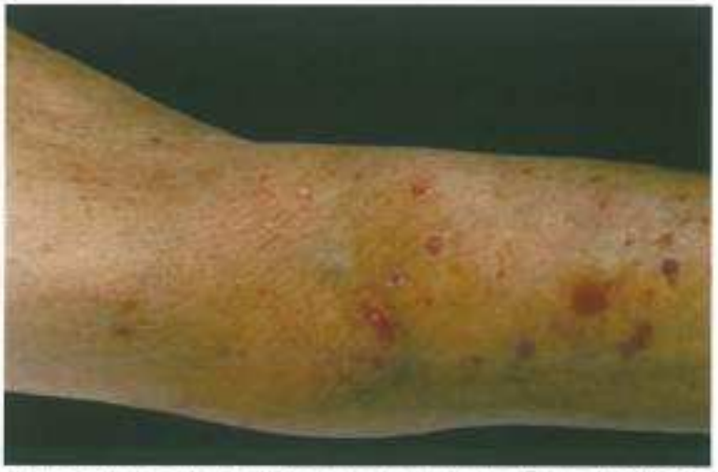


Fig. 5.54 Psoriasis treated with superpotent steroids. Purpura, atrophy and abnormal visibility of the vasculature have resulted from the habitual use of a topical steroid. The psoriasis is still present.

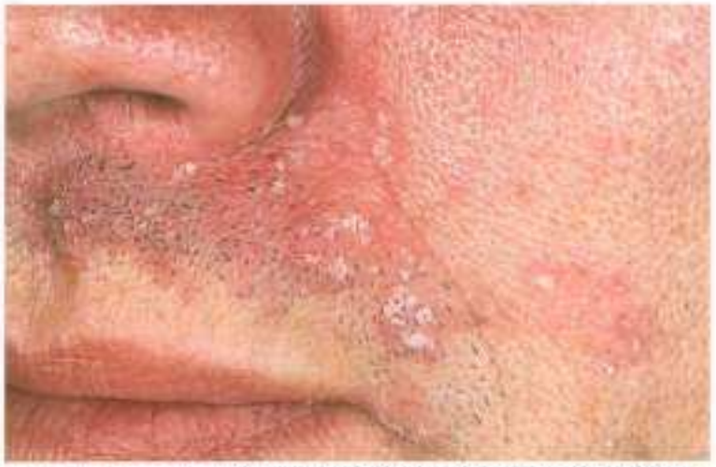


Fig. 5.55 Sebopsoriasis. Although the distribution around the nose is typical of seborrhoeic eczema, recalcitrant disease often turns out to be psoriasis. Note the thick scale and red colour. Topical steroids may be used.

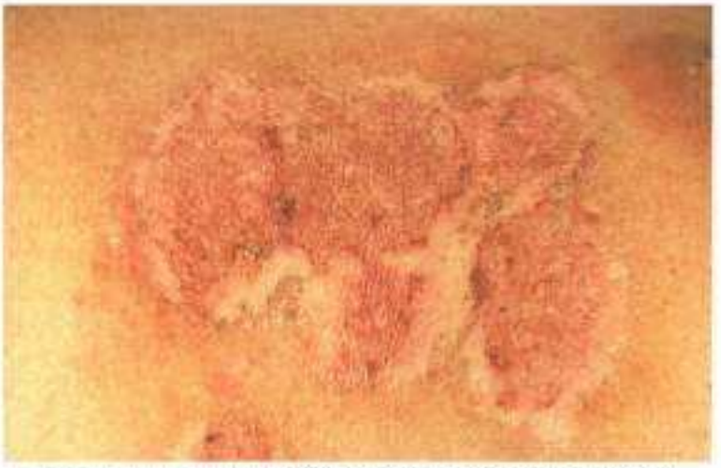


Fig. 5.56 Dithranol treatment. Dithranol stains the skin brown but this clears within 10 days of cessation of treatment.

either limited involvement or psoriasis of the scalp, face (Fig. 5.55) and flexures. Hydrocortisone is ineffective in psoriasis and so, except for the face, are the moderately potent steroids.

Topical steroids are often prescribed in combination with tar or dithranol.

- **With tar** Proprietary preparations are available that are useful for the face and genitalia. Combinations, for example 3% coal tar solution mixed with a potent steroid for the body or a moderately potent steroid for the face can be made up extemporaneously.
- **With dithranol** There are no proprietary versions of this, but there is good evidence that 0.1% dithranol with subsequent increments of 0.25 and 0.5% in quarter-strength clobetasol propionate may be effective.

Vitamin D analogues

Human keratinocytes have receptors for 1,25-dihydroxyvitamin D3 (calcitriol), which is produced by the kidney. This hormone induces terminal differentiation and inhibits the proliferation of keratinocytes. It is quite effective topically and systemically. The synthetic analogues calcipotriol and 1,24-dihydroxyvitamin D3 (tacalcitol) are also effective topically. Local irritation is common. All have the potential to affect calcium homoeostasis. Applications of more than 100 g increase 24-hour urinary calcium levels and more than 300 g a week causes a significant rise in serum and urinary calcium levels.

Topical retinoids

Tazarotene is a topical nuclear receptor-specific acetyleic retinoid. Its primary target is the keratinocyte, and it probably has a direct effect on gene expression. It normalizes the abnormal differentiation that occurs in psoriasis and has an antiproliferative effect on the keratinocyte. However, it also decreases the expression of inflammatory markers on the keratinocyte, thereby decreasing the influx of inflammatory immune cells into the skin. As a 0.1 or 0.05% gel, it is beneficial in psoriasis, although it may cause local skin irritation. It does not appear to have any systemic effect.

Dithranol (anthralin, Cignolin)

Dithranol is a derivative of chrysarobin derived from the bark of the araroba tree, which is indigenous to South America and southern Asia. Formerly known as Goa powder, because it was first exported from Brazil to the Portuguese colony of Goa in India, it was originally used in the treatment of ringworm but was serendipitously found to be effective in psoriasis. It acts as an antimitotic agent. Dithranol is made up in Lassar's paste (2% salicylic acid, 25% starch, 25% zinc oxide in soft paraffin) and applied daily, starting at 0.1% and gradually increasing through 0.25% to 0.5%; occasionally higher concentrations are prescribed. It must be used with care as:

- it stains clothing and sheets, as well as bath enamel
- it stains the skin temporarily, for about 10 days (Fig. 5.56)
- it may cause erythema and burning of the normal skin (Fig. 5.57).

Dithranol should not be used:

- in the flexures, because burning is inevitable
- on the face, except under supervision, starting at a very low dose (0.05%)
- on inflamed psoriasis, for it may induce pustulation.

Dithranol should be applied by a nurse and covered with talc (to reduce spreading onto normal skin) and tube-gauze dressings. It is washed off the

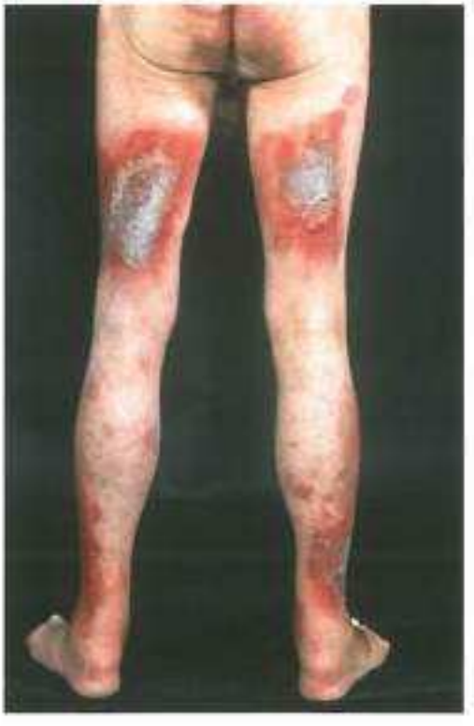


Fig. 5.57 Dithranol treatment. The wrong concentration and spreading onto normal skin results in burning and inflammation.

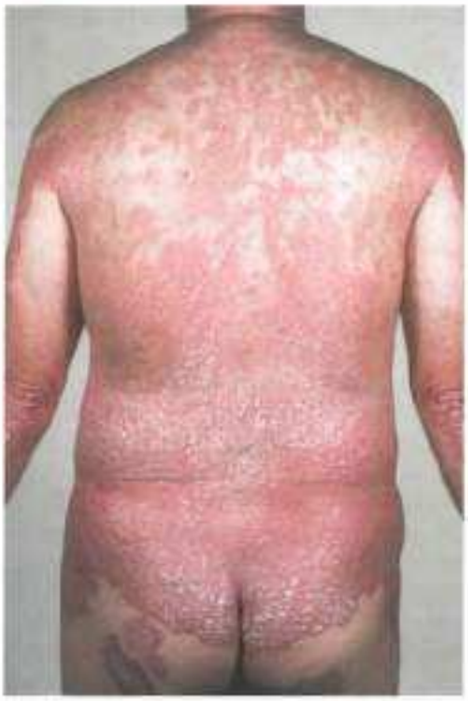


Fig. 5.58 Extensive psoriasis. Topical treatments are ineffective in widespread psoriasis like this. Patients require phototherapy or systemic therapy.

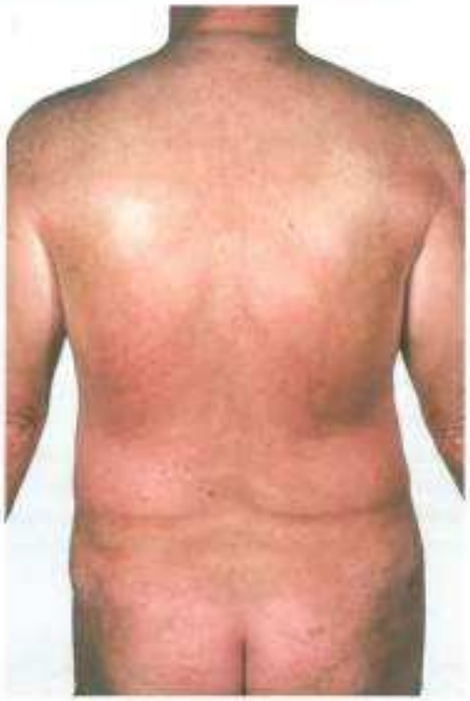


Fig. 5.59 Psoriasis treated with narrowband UVB. This is an effective treatment for the patient in Fig. 5.58 and has many advantages over PUVA including less risk of cutaneous carcinogenesis.

next day with arachis oil. If combined with a tar soap (for example 20% coal tar in emulsifying ointment) and phototherapy it is known as the Ingram regimen and is suitable for chronic stable psoriasis. Most patients are free of the disease after 3 weeks in hospital, but within a year 50% will have relapsed.

Several proprietary preparations are available, including a non-staining derivative (Micanol). 'Short contact therapy' (leaving dithranol on for 30 minutes only) is ideal for daycare centres; it permits the patient to continue working without the expensive and time-wasting practice of a 3-week stay in hospital.

Ultraviolet light

Many patients observe that their psoriasis improves in the sun. It is, therefore, logical to use artificial methods of UV irradiation. Broadband UVB (290–320 nm) and the Theraktin UV lamp (which also delivers UVC (< 290 nm), which causes burning more quickly than UVB and, therefore, limits the potential time of exposure to UVB) have been replaced by narrowband UVB (311–313 nm). This is produced by TL-01 lamps. Their development is based on action spectra studies, which have shown that longer UVB wavelengths have the best ratio of antipsoriatic (Figs 5.58 and 5.59) to erythemogenic activity (Fig. 5.60). This has been confirmed clinically by bilateral comparison studies, in which there was faster clearing, less burning and longer remissions with narrowband UVB than with conventional broadband UV. There are two methods of use. In the first, the MED (minimum dose to produce a faint erythema) is determined and treatment is started at 70% of this, increasing by 10–20% increments at each subsequent treatment. In the second, a standard starting dose is used with stepwise increments depending on the patient's response. The treatment is given two or three times a week for 18 or more treatments in total. Although PUVA is probably superior in improving the psoriasis area and severity index (PASI), the absence of psoralen-related nausea, the ability to use it in pregnancy and the opportunity to dispense with 24-hour eye protection are distinct advantages. Its safety is not established in that narrowband UVB does produce a similar degree of sunburn cells as PUVA, but it may be safer because the number of pyrimidine dimers produced in fibroblasts is less than with PUVA. The safety of broadband UVB is well established and there has been little or no observed risk of skin cancer, probably because the type of DNA lesion produced by broadband UVB is less error-prone than that for PUVA.

Use of UVA (320–400 nm) on its own, in the form of sunbeds, has no effect in psoriasis. However, climatotherapy is used at the Dead Sea, which at 390 m below sea level is the lowest place on earth. The UV light there is mainly UVA and of a very high intensity but the sunburn spectrum is very weak because of the continuous haze over the water. The sea is rich in natural minerals and salts, and certainly many patients derive benefit from a 3-week stay in the area.

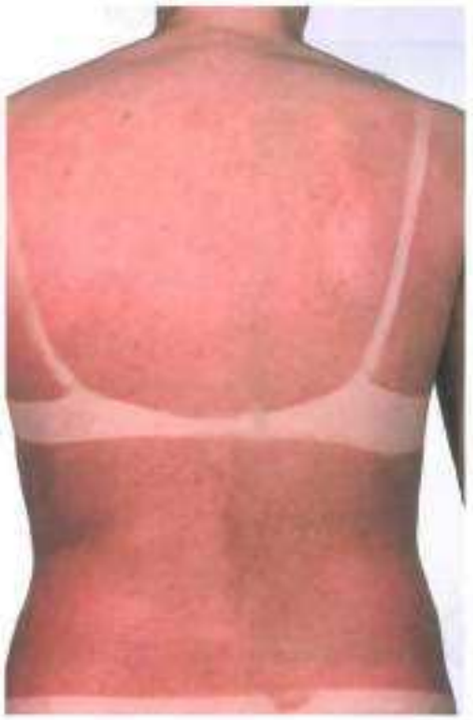


Fig. 5.60 Psoriasis. Ultraviolet light therapy is effective in many patients but overradiation resulting in painful 'sunburn' must be avoided by careful attention to dosage and skin type.

Systemic Therapy

The decision to use systemic therapy is always difficult, for it is generally a long-term commitment as the disease usually (but not always) returns to its previous state on cessation of therapy; systemic agents also have potential side-effects, and patients require constant supervision. Indications for systemic therapy include:

Definite	Erythrodermic psoriasis
	Generalized pustular psoriasis
Relative	Subacute psoriasis
	Extensive psoriasis
	In the elderly
	Where topical therapy has failed
	Where there is interference with function (psoriasis of the palms and soles), personal happiness or livelihood

Although there are a number of possible systemic agents, those most commonly used by specialists are discussed below. They are all effective, but there is considerable individual variation in tolerance and response. Rotational use of these agents in order to provide rest periods is now being advocated.

Methotrexate

Methotrexate is probably the most commonly used systemic therapy for psoriasis. It is an effective treatment (Figs 5.61 and 5.62) that has been available since the early 1950s, when it was noted that psoriatics who were being treated for leukaemia with aminopterin (a related drug) were cleared of their skin disease.

Dose schedules

Methotrexate is usually given in a dose of 0.2–0.4 mg/kg, which, on average, means about 25 mg once a week. It is important to start at 2.5–5 mg as a test dose in order to detect idiosyncratic myelosuppression. This occurs within 7 to 10 days and is rare, but a full blood count is important at this time. Thereafter, the dose can be increased. The drug is sometimes given in divided doses over a 36-hour period once a week, based on a knowledge of the kinetics of the epidermal cell cycle in psoriasis. Much lower doses are used in generalized pustular psoriasis. Methotrexate causes a profound depression of the enhanced polymorphonuclear leucocyte and monocyte chemotaxis of psoriasis after about 48 hours and normalizes it with long-term treatment.

Drug interactions

Certain drugs interfere with the action of methotrexate, by reducing its elimination (e.g. aspirin and some non-steroidal anti-inflammatory drugs), by displacing it from binding sites on serum proteins (e.g. barbiturates, sulphonylureas and tetracyclines) or by having an additive or synergistic action (e.g. septrin and alcohol). Lists of these agents are available.

Side-effects

Nausea is common: an antiemetic 2 hours before the methotrexate, folic acid 5 mg daily or taking the drug at night may prevent this. Occasionally, it causes headaches and gastrointestinal haemorrhage. It is a cytotoxic drug and bone marrow toxicity is a potential hazard, but in the dose prescribed for psoriasis it rarely gives rise to haematological side-effects. From time to time, however, mistakes are made and, in error, the patient is given the drug daily, with very serious consequences. Methotrexate is excreted by the kidney. Hepatotoxicity is uncommon in those who drink small quantities of alcohol, but a full blood count, liver and renal function should be routinely tested. Liver biopsy is rarely indicated. Serological markers, particularly the amino-terminal propeptide of type III procollagen (PIIINP), are now being used as a screening test for hepatic fibrosis. Oligospermia is a side-effect, but although fertility is decreased, any child of a male patient taking methotrexate should be quite normal. The drug is teratogenic in early pregnancy, and so all female patients should take contraceptive precautions if they are sexually active. Conception is probably safe 3 months after cessation of systemic therapy in either sex, but patients should be advised to wait longer.

Photochemotherapy (PUVA)

Long-wave UVA is ineffective, however, in combination with the photosensitizers 8-methoxypsoralen (MOP) or 5-MOP, orally or topically, it is highly effective.

PUVA with systemic psoralens

The dose of UVA (joules/cm^2) depends upon the patient's skin type. PUVA is usually given two to three times a week for 18–20 treatments to obtain

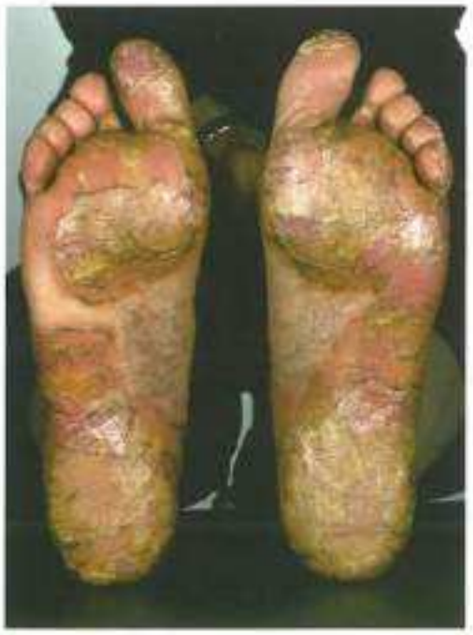


Fig. 5.61 Psoriasis of the feet before treatment with methotrexate. Topical therapy is often ineffective and yet psoriasis may interfere with mobility. Systemic therapy with methotrexate or retinoids should be considered.

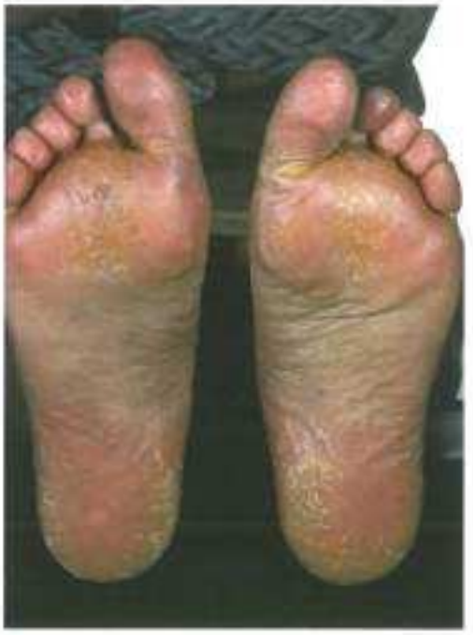


Fig. 5.62 Psoriasis of the feet after methotrexate. The drug has been invaluable in preserving function. It is hepatotoxic and myelosuppressive if certain guidelines are not followed.

complete clearance of the psoriasis. Previously, maintenance therapy once every 10 days was routine, but this is now unusual because the risk of cutaneous malignancy is cumulative and becomes highly significant after a total dose of 1200 joules/cm² UVA, or more than 260 treatments, with an estimated 11-fold increase in squamous cell carcinomas (Fig. 5.63). Types 1 and 2 skin have the greatest risk. Multiple tumours and tumours in non-solar-exposed sites (for example, the palms and soles) seem to be common. Genital cutaneous malignancies have been particularly described in males, and it is advisable that this area is physically protected when using PUVA (although this is problematic if the patient has genital psoriasis and wants the area treated). An early sign of PUVA-induced photodamage is the appearance of lentigines. These are characterized histologically by large, sometimes cytologically atypical, melanocytes. Photochemotherapy is effective in dark skins, although the resultant increase in pigmentation is sometimes unacceptable.

PUVA may be used in pregnancy. Although theoretically it is mutagenic and teratogenic, it has not been shown to carry any significant risk. It is most important that the patient wears photoprotective glasses from the moment that they take their 8-MOP tablets until 24 hours later, as cataracts and other ocular abnormalities are otherwise likely to be hazards. The therapy is no help for inaccessible body sites, such as flexures (Fig. 5.64), and the scalp. The most common side-effects are itching and burning of the skin. The former can be eased by the regular use of bath additives and oils. Emollients do have a photoprotective action, especially for UVB but also for PUVA, particularly in the form of creams, lotions and ointments; consequently, they should be avoided on the day of treatment.

PUVA with topical psoralens

Psoralens may be applied topically or added to a bath and followed by UVA. The advantage over systemic therapy is that glasses do not have to be worn and there is no nausea. Care must be taken because burning is common.

PUVA with dihydroxyacetone

Dihydroxyacetone-enhanced photochemotherapy (Turbo-PUVA), has been described. Dihydroxyacetone is a colourless three-carbon sugar that is present in 'sunless' tanning products. It binds covalently to stratum corneum proteins and polymerizes to form a brown pigment, which is lost by corneocyte sloughing. It acts as a photoprotectant to the normal skin and permits higher doses of PUVA to be delivered to the psoriasis, and hence faster clearing.

Retinoids

Vitamin A deficiency results in reversible dry skin, follicular hyperkeratosis and epithelial squamous metaplasia. As vitamin A therapy was known to be beneficial in acne, and to a lesser extent in psoriasis, but unacceptable because of toxicity (hypervitaminosis A), a screening programme for synthetic analogues of vitamin A with an improved risk–benefit ratio was instituted for the treatment of acne, ichthyosis and psoriasis. Etretinate (Tigason) was the first of the oral agents found to be effective. It is extremely lipophilic and is stored in adipose tissue, from which it is slowly released. It is the ethyl ester of acitretin, which has superseded it because it is 50 times less lipophilic and is, therefore, eliminated more rapidly and since both are teratogens, there is, theoretically, a much shorter post-therapy period when contraception is required.

Side-effects

All patients suffer from dryness of the lips and skin during therapy, but this is rarely a significant problem. Peeling of the fingers and toes, particularly the tips, and burning of the skin with or without erythema, particularly of the face, may occasionally occur. Diffuse interosseous calcification is rare but has been observed. Retinoids should not be given to patients with active liver disease, and it is known that most patients have increases in triglycerides and probably a quarter have increases in cholesterol during therapy. Etretinate and acitretin are teratogens and must not be given during pregnancy. The recommended post-therapy contraceptive period for etretinate is 3 years. Acitretin was introduced because it was originally thought that a short, 2-month post-therapy contraceptive period was all that was required. It is now recognized that etretinate may be formed from acitretin in the presence of alcohol, but the pharmacokinetic advantages of acitretin over etretinate may still hold true for women who strictly avoid alcohol during therapy and for 2 months thereafter. Acitretin normalizes epidermal cell proliferation, differentiation and keratinization. It interferes with epidermal growth factor genes and has immunomodulatory properties by inhibiting dermal microvascular endothelial cells and neutrophil migration.

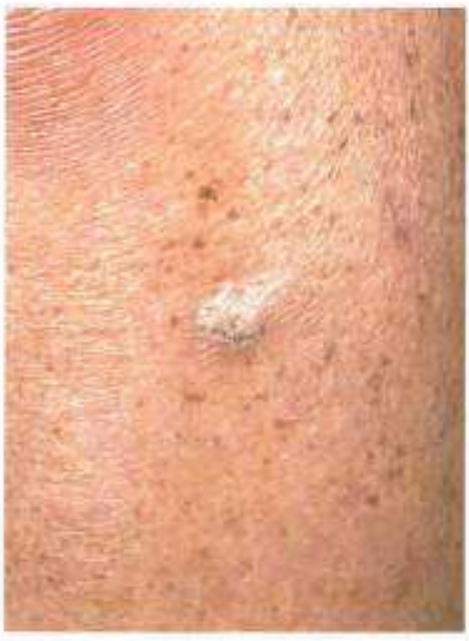


Fig. 5.63 Lentigines and squamous cell carcinoma from PUVA (a psoralen plus ultraviolet A) treatment. Systemic photochemotherapy is effective in psoriasis but is an established cutaneous carcinogen with cumulative doses and a high-risk skin type. An early sign of photodamage is the appearance of lentigines.

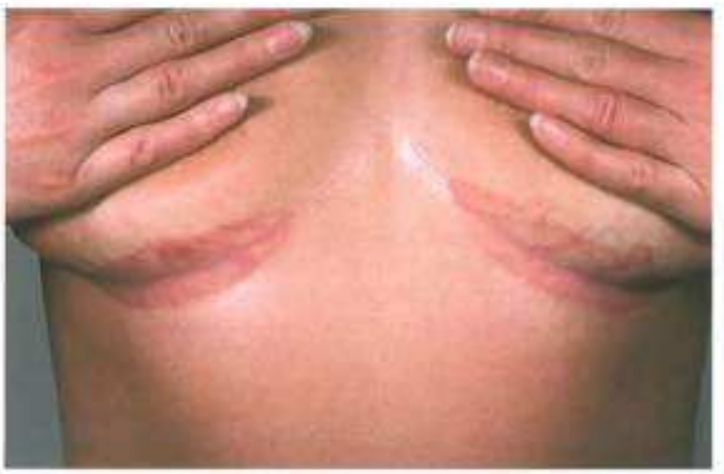


Fig. 5.64 Sanctuary site psoriasis and PUVA (a psoralen plus ultraviolet A). One disadvantage of PUVA is that certain sites are shielded from the ultraviolet light.

Dose schedule

Etretinate is given in a dose of 1 mg/kg and acitretin in doses of 10–30 mg daily. Both etretinate and acitretin are particularly effective in erythrodermic and generalized pustular psoriasis, but also in extensive psoriasis in the elderly. Acitretin is indicated either alone or in combination with zidovudine for psoriasis associated with HIV disease. Some centres use the retinoids on their own and others use them in combination with PUVA (RePUVA), the rationale being that this reduces the amount of UV light required. Similarly, the retinoids have been used in combination with UVB.

Ciclosporin and tacrolimus

Ciclosporin and tacrolimus are potent immunosuppressives used to prevent rejection following organ transplantation. Ciclosporin inhibits production of IFN-γ and IL-2 by $CD4^+$ T cells and subsequent T lymphocyte proliferation. It also has a definite but less marked effect in suppressing antigen-presenting cell and monocyte function. There is no real evidence that ciclosporin has any direct antiproliferative effect on the keratinocytes. Both drugs are effective in psoriasis (although not topically) but do have a number of potentially toxic side-effects and must be used with great care.

Side-effects

Renal dysfunction, both functional with reduced glomerulofiltration rates and anatomic with interstitial fibrosis and renal tubular atrophy, may occur. It is important to reduce the dosage if the serum creatinine level rises 30% above baseline (even if it is still within normal limits). Hypertension (probably secondary to the above), hirsutism, gingival hypertrophy, headache, paraesthesia, musculoskeletal and gastrointestinal side-effects may occur. There is a risk of non-Hodgkin's lymphoma and a considerable risk of skin carcinogenesis, particularly if the patient has previously been treated with PUVA, UV light or, to a lesser extent, methotrexate or tar. Serum bilirubin is usually increased during treatment but is not a problem unless there are other liver function test abnormalities. Uric acid levels, cholesterol and triglycerides may also increase. Drug interactions are frequent. Lists are available of drugs that may potentiate renal dysfunction or may increase or lower ciclosporin levels, and these should be checked.

Dose schedules

Either low- or high-dose regimens of ciclosporin are used. The low dose starts at 2.5 mg/kg daily and is increased by 0.5–1.0 mg/kg per day every 2 weeks, to the maximum recommended dose of 5 mg/kg per day. The high-dose regimen starts at 5 mg/kg daily. It is well tolerated, especially for short-term use, and higher daily doses are more effective than 2.5 mg/kg. It is doubtful whether ciclosporin or tacrolimus will serve as a long-term monotherapy because of the high risk of nephrotoxicity and hypertension, but they may be very useful as part of a rotational scheme of treatments.

Other modes of systemic therapy

Azathioprine and hydroxyurea are second-line alternatives. Azathioprine is a potent immunosuppressant and there are fears of the long-term risk of the development of lymphoma. Hydroxyurea is effective in psoriasis but less so than methotrexate; it does cause much more short-term marrow toxicity than methotrexate but does not have the gastrointestinal upset and the potential hepatotoxicity of the latter. In early trials in the 1970s, mycophenolic acid was shown to be effective in psoriasis, but was abandoned because of gastrointestinal side-effects. Its precursor mycophenolate mofetil is a potent immunosuppressant used to prevent acute renal graft rejection. It is useful in psoriasis, especially those who develop ciclosporin-induced nephrotoxicity. The drug potently and selectively inhibits the de novo pathway of purine synthesis in T and B cells. Because lymphocytes rely on the de novo rather than the salvage pathways, the drug minimizes unwanted side-effects on other cell types. Other allograft rejection drugs, such as sirolimus (rapamycin), a macrolide immunosuppressant, have also been reported as being effective in psoriasis.

Biologics

After initial contact with an unknown antigen (signal 1) a subset of T cells (primarily $CD4^+$ cells in the dermis and $CD8^+$ in the epidermis, which migrate there from the circulation) are activated by antigen-presenting cells (APCs) to form memory T cells (CD45RO). On secondary activation from the APC (signal 2) possibly by an autoantigen, these cells proliferate and transit from the lymph nodes to the skin where they secrete cytokines, primarily of the Th1 type (IL2 and IFN-γ). Biologics (selective immunomodulatory drugs) can target some of these steps. They represent the value of the advances in understanding the molecular pathogenesis of psoriasis. They are, however, not without risk.

Opportunistic infections (tuberculosis, histoplasmosis, aspergillosis, listeriosis and pneumocystis), an increased risk of non-Hodgkin's lymphoma, immune-mediated thrombocytopenia, demyelinating disorders and autoantibodies formation, especially with the anti TNF-α therapies, have all given cause for concern.

Reduction in the number of memory T cells

Alefacept (Amevive) is a recombinant dimeric fusion protein, which binds to CD2 on memory effector T cells and reduces them. It reduces $CD4^+$ cells and therefore is not indicated in HIV-driven psoriasis. It is given intramuscularly or intravenously. Only half of the patients respond but there is no increase in unwanted infections or cytokine release syndrome (fever, hypotension, abdominal symptoms and toxic erythema).

Inhibition of T cell activation and migration

Efalizumab (Raptiva) is a recombinant humanized monoclonal IgG1 antibody against CD 11a subunit of LFA-1 (lymphocyte function associated antigen-1) and blocks T cell adhesion to endothelial cells, T cell migration into inflamed skin and activation of T cells. It was given subcutaneously, was effective but has been withdrawn because of concern over progressive multifocal leukoencephalopathy (a rare opportunistic infection of the CNS caused by the JC virus).

Binding and blocking of post secretory cytokines (Tumour necrosis factor)

Adalimumab (Humira) is the first fully human anti TNF-α monoclonal antibody. It binds soluble and membrane bound TNF-α. It is given subcutaneously.

Etanercept (Enbrel) is a recombinant human TNF-α receptor protein fused with the Fc portion of IgG1. It is given subcutaneously. It works more slowly than Adalimumab or Infliximab. Injection site reactions are not uncommon.

Infliximab (Remicade) is a chimeric (murine and human) antibody. It binds soluble and transmembrane TNF-α molecules, is given intravenously and produces a rapid response. It is often given with methotrexate to reduce the formation of antibodies to infliximab. Screening for tuberculosis is necessary because there is an increased risk of this and other infection. Infusion reactions (fever, chills, hypotension, dyspnoea and urticaria) may occur. There may be increased titres of the antinuclear factor and, rarely, a lupus syndrome and of neutralizing antibodies and serum sickness.

Interleukin binding

Ustekinumab is a fully humanized IgG1 monoclonal which prevents IL-12 and 23 from binding their receptor proteins on the surface of immune cells.

Pityriasis rosea and pityriasis rubra pilaris

6

Pityriasis rosea and pityriasis rubra pilaris belong to a set of disorders known as papulosquamous diseases. This simply means that the eruption is scaly and consists of papules, which may or may not coalesce into plaques. Eczema, psoriasis, parapsoriasis, secondary syphilis and some drug eruptions are other examples of papulosquamous disorders but are described elsewhere as much is known about their aetiology. Pityriasis rosea and pityriasis rubra pilaris are brought together here for convenience since their causes are unknown, although eventually, as their aetiology is discerned, their inclusion in other chapters may be more appropriate.

Fig. 6.1 Pityriasis rosea. Pityriasis rosea is common in the young including children. The lesions are oval, have a peripheral scale and are uniform in size, other than the larger 'herald patch' seen on the medial side of the left scapula.

Pityriasis rosea

An eruption lasting a few weeks that begins as a large solitary so-called 'herald' patch followed by a rapidly evolving rash on the trunk.

Aetiology

Pityriasis rosea is common, particularly in the autumn and winter. It affects women possibly a little more frequently than men and is more usual between the ages of 10 (Figs 6.1 and 6.2) and 35 years, although it has been reported in the very young and the very old. The histology is that of an eczema, but its aetiology is obscure. Most favour a viral cause, because second attacks are unusual, which suggests the acquisition of immunity. Small epidemics have occurred and dermatologists are said to be four times more at risk than their ENT colleagues. However, outbreaks among associates of the patient are exceptional. Interest has centred on herpes simplex virus type 7 (HHV-7), an ubiquitous virus that exhibits tropism for the $CD4^+$ T cell, and to a lesser degree on HHV-6, but nothing has been proven.

Clinical Features

Symptoms

The patient describes an asymptomatic rash all over the torso but may remember an initial solitary large patch. It is occasionally very itchy.

Morphology

The initial lesion is a pink (rosea) oval patch approximately 3–6 cm in diameter (Fig. 6.3). It has a scale (pityriasis), which occurs like a collarette towards the periphery but not at the margin of the lesion. It is known as the herald patch because it is followed after a few days by an eruption of

Fig. 6.2 Pityriasis rosea. The herald patch is the hallmark for diagnosis: it is the initial lesion and is larger than the subsequent patches. This is a view of the Afro-Caribbean boy in Fig. 6.1.

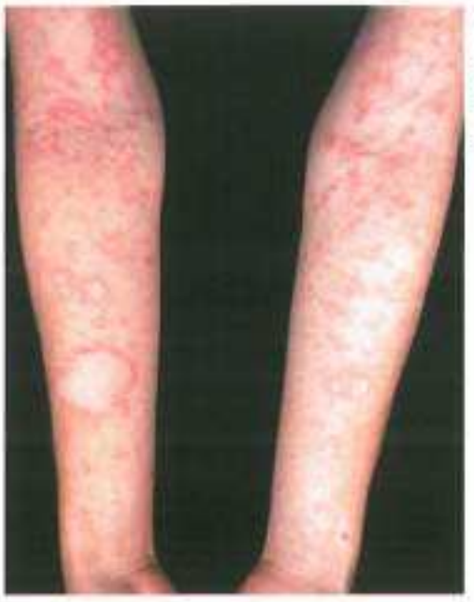


Fig. 6.3 Pityriasis rosea. The large herald patch is present on the patient's right forearm. The subsequent lesions are much smaller.

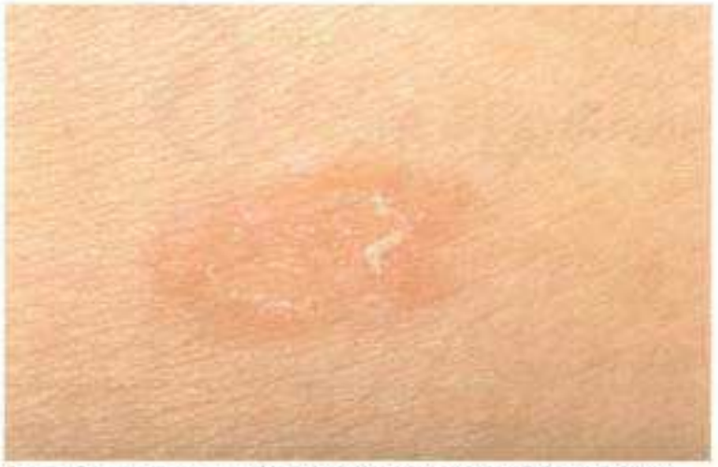


Fig. 6.4 Pityriasis rosea. The herald patch is the first to appear and is larger than subsequent patches. There is a noticeable collarette of scale towards the periphery but not at the margin of the patch.

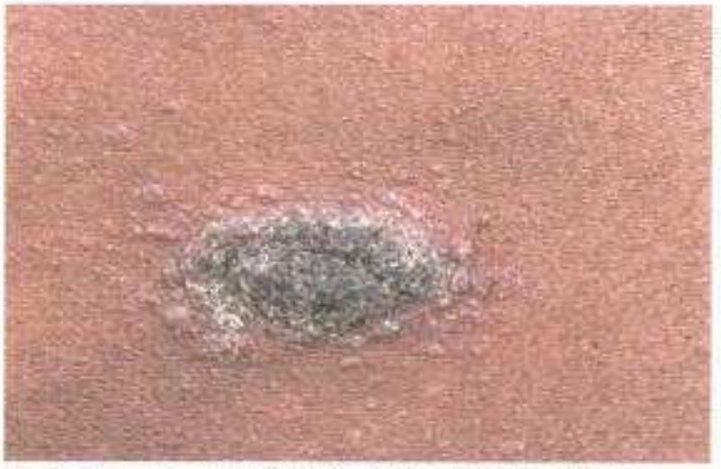


Fig. 6.5 Pityriasis rosea. In this herald patch in an Afro-Caribbean there is pigmentation in the older central part of the patch but the pink margin is still visible. Note the papules around the herald patch. The initial lesion may be papular.

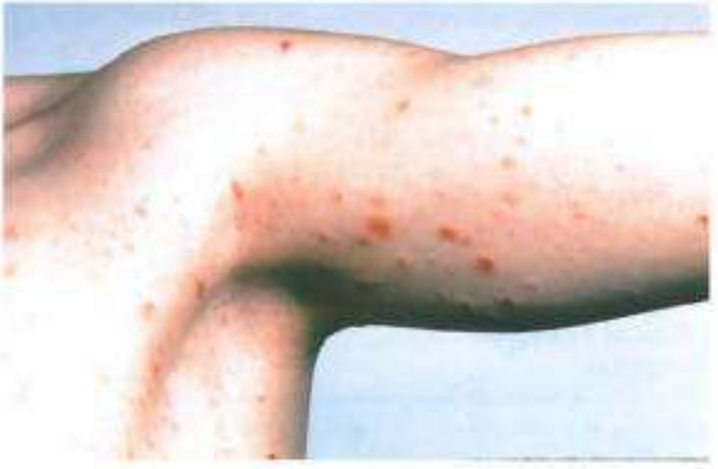


Fig. 6.6 Pityriasis rosea. The subsequent lesions commence as pink papules, which may be mistaken for insect bites, but become oval red scaly patches later.

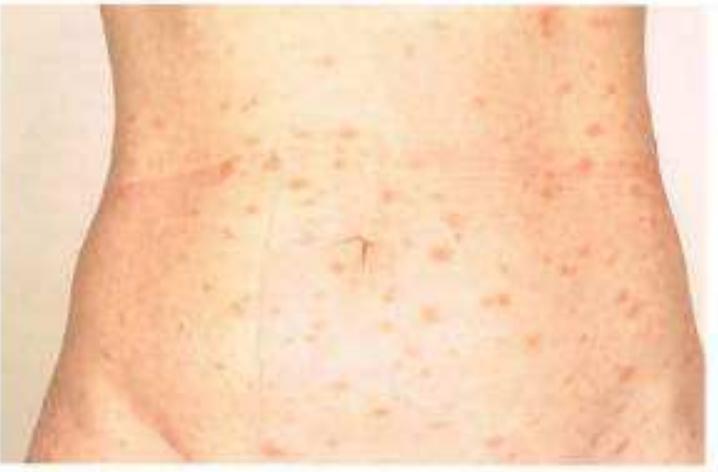


Fig. 6.7 Pityriasis rosea. The patches are quite obviously pink in a Caucasian skin. They are oval and scattered symmetrically over the trunk.

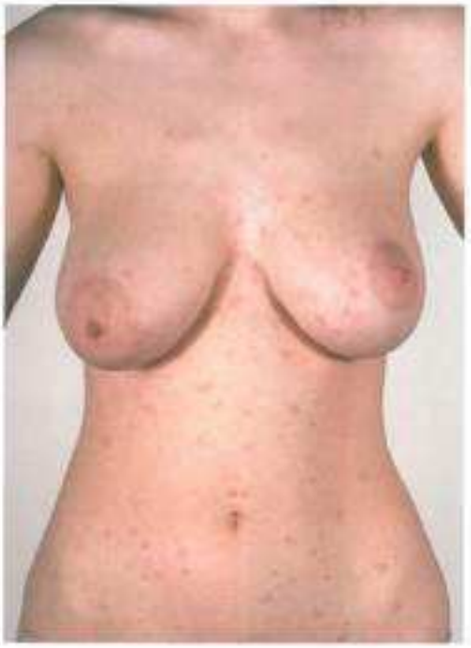


Fig. 6.8 Pityriasis rosea. The eruption affects the torso. The forearms and shins are usually but not always spared. The face is rarely involved.

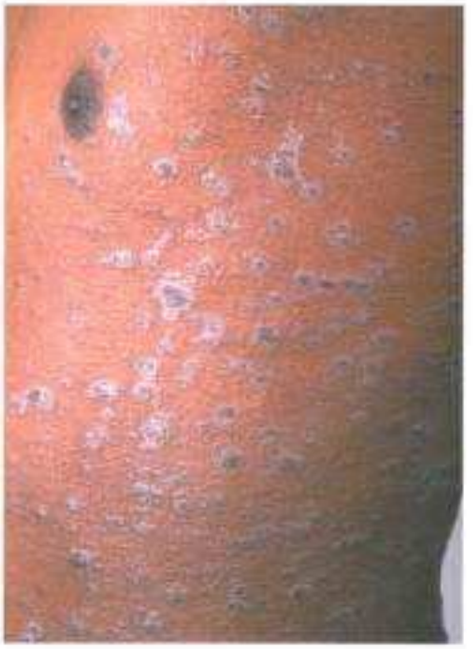


Fig. 6.9 Pityriasis rosea. In pigmented skins, the pink colour is less easy to discern but the patches are oval with peripheral scaling.

similar but much smaller lesions. It occurs anywhere on the skin within the area usually affected by the condition. The herald patch (Figs 6.4 and 6.5) is one of the enigmas of dermatology as it occurs in no other skin disease. The earliest lesions of the subsequent eruption are pink papules, which are occasionally mistaken for insect bites (Fig. 6.6), but the papule readily spreads outwards to produce oval macules that vary from 1 to 3 cm in size. This stretching outwards produces the characteristic collarette of scale.

Distribution

The distribution of the rash is essentially that of a T-shirt and shorts; indeed Lassar thought that an organism in clothing might be its cause, but this has not been confirmed by patch tests. Thus the torso (Fig. 6.7), abdomen (Fig. 6.8), chest (Fig. 6.9), back, upper arms, thighs and neck (Fig. 6.10) are affected. The lesions occur in a symmetrical distribution. The patient is otherwise completely well and there are no preceding symptoms. The condition lasts approximately 6 weeks and then fades, rarely recurring.

For the specialist, the diagnosis is generally straightforward, since the patient is usually seen after the rash has spread and may volunteer the information that one patch appeared first. However, for the general practitioner the diagnosis can be more difficult because the herald patch may remain solitary for several days or even weeks before subsequent lesions appear. Not surprisingly, in view of its oval or ring shape, it may be misdiagnosed as ringworm.

Occasionally the eruption is not quite true to form, which may cause confusion.

- **The herald patch** This is sometimes absent.
- **Suntan** In patients with a suntan, it may be restricted to localized sun-spared areas (Figs 6.11 and 6.12), such as the breast, axillae, pubis and buttocks.
- **The lesions** These may be few and large (Fig. 6.13), often localized to one region of the body such as the axillae and groin. This eruption occurs in adults and may persist for several months. It is sometimes known as *pityriasis circinata et marginata of Vidal*.

Fig. 6.10 Pityriasis rosea. The neck is usually involved but the face is rarely affected, and then only to a minor degree. Note the oval shape of the lesions, peripheral scaling and central hyperpigmentation.

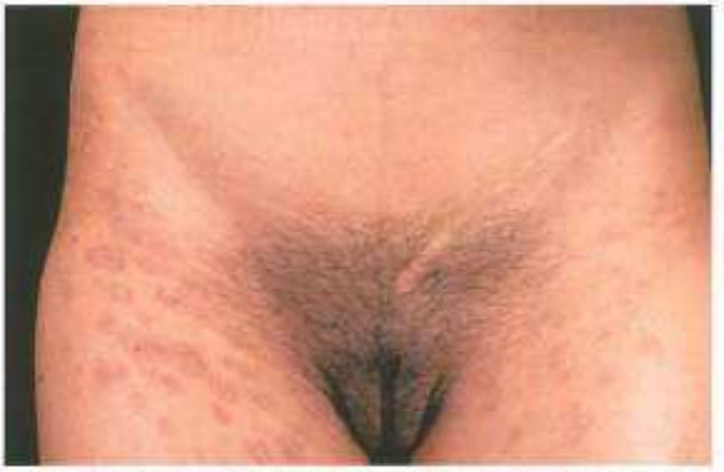


Fig. 6.11 Pityriasis rosea. Occasionally the eruption is limited to sun-spared areas of the skin such as the breasts, axillae and groin. The collarette of scale is characteristic. (By courtesy of the Institute of Dermatology.)

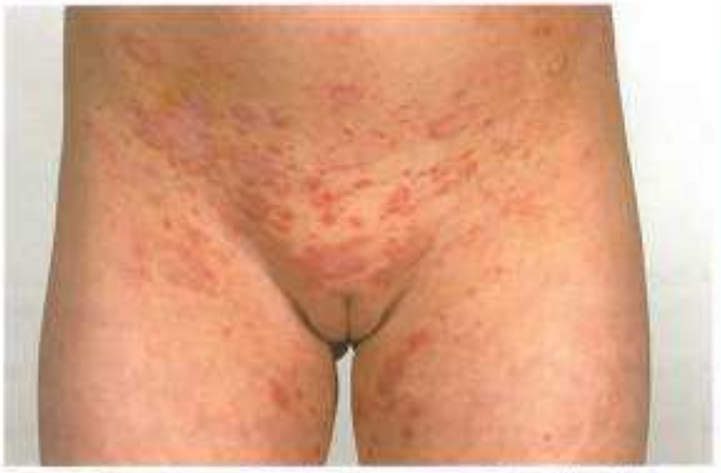


Fig. 6.12 Pityriasis rosea. The pink oval patches are clearly visible. Lesions predominantly in the axillae and groin are quite common in children. The rash lasts about 6 weeks. Recurrences are unusual.

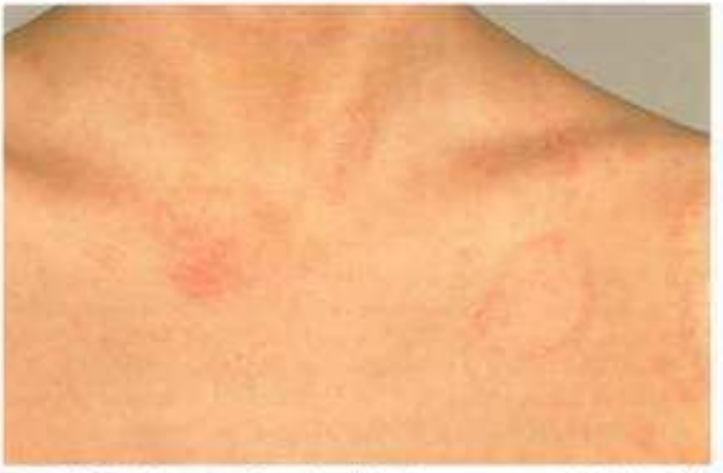


Fig. 6.13 Pityriasis rosea. Sometimes the lesions are sparse and quite localized. The general morphology is that of pityriasis rosea but the lesions are much larger than usual.

Fig. 6.14 Eczematide. This variant of pityriasis rosea occurs in black skins and is more widespread and persistent although eventually clearing after some months.

Fig. 6.15 Postinflammatory hypopigmentation. Temporary loss of pigment occurs particularly following eczema in dark skins including pityriasis rosea as in this patient.

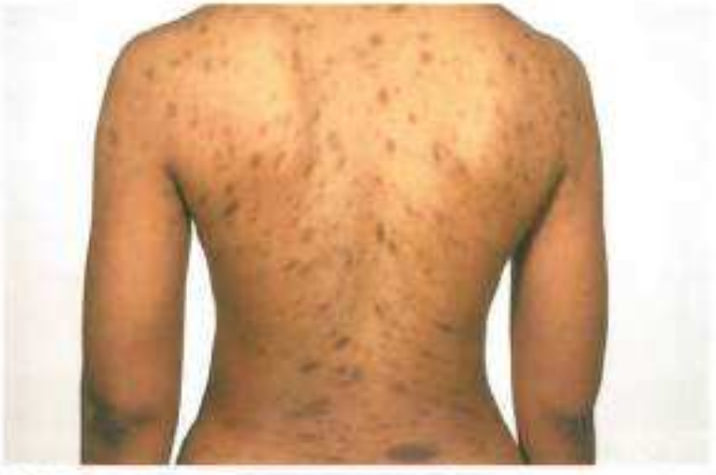


Fig. 6.16 Pityriasis rosea. Hyperpigmentation is a frequent consequence of pityriasis rosea in a black skin. Note the herald patch over her right hip. It is larger than any of the other patches.

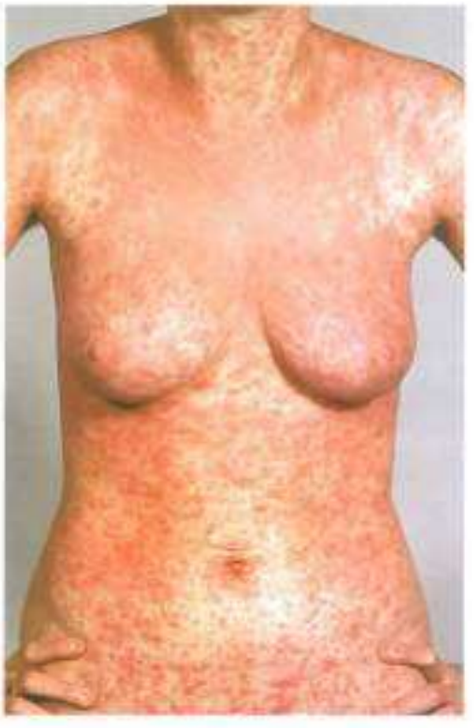


Fig. 6.17 Pityriasis rosea. Sometimes the eruption is very florid indeed with coalescence of the pink patches.

- **Dark skin** The eruption may be more widespread, including the forearms and lower legs. However, the morphology of the lesions remains the same, although the pinkness may be difficult or impossible to discern. This variant is more persistent and lasts several months. It is known as an *eczematide* (Fig. 6.14). In pigmented skins, postinflammatory hypopigmentation (Fig. 6.15) or hyperpigmentation (Fig. 6.16) may occur. This takes many months to recover.
- **Distribution** The disease may occur in areas usually unaffected in pityriasis rosea, such as the face and extremities, while sparing the rest of the body. This is known as *inverse pityriasis rosea*.
- **Morphology** This may vary, being predominantly papular or even vesicular and very occasionally purpuric.
- **The eruption** This may be florid (Fig. 6.17) with coalescence of the pink patches.

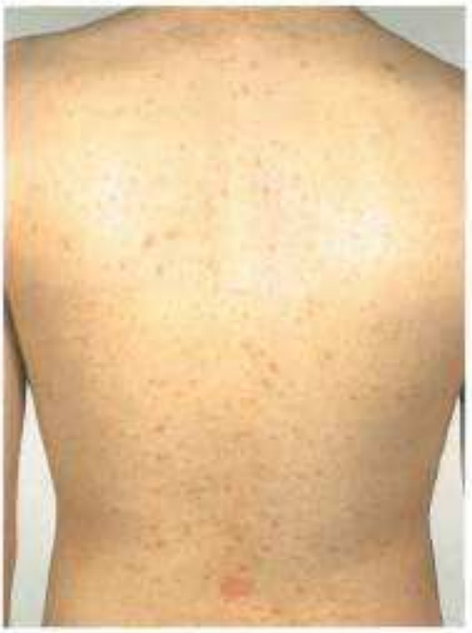


Fig. 6.18 Pityriasis rosea. In Caucasian skin the pink colour is clear and postinflammatory hyperpigmentation unusual (compare with Fig. 6.16). Note the herald patch over the lower back.

Fig. 6.19 Tinea. In human ringworm the margin is slightly raised and scaly. The central part of the lesion, by contrast, shows almost normal skin. Scrapings of the scales mounted in potash should reveal fungal hyphae.

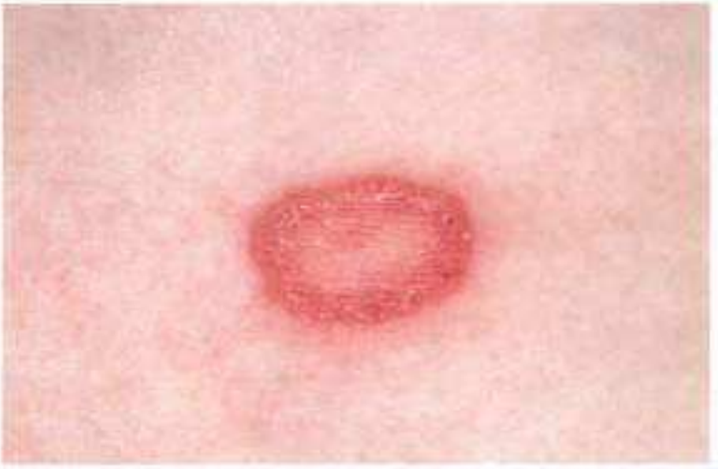


Fig. 6.20 Tinea. In ringworm, particularly animal ringworm, the margin of the annular patch is more inflammatory, scaly and raised than in the herald patch with a tendency to central healing.

Differential Diagnosis

The herald patch

The major differential diagnosis of the herald patch (Fig. 6.18) on its own is ringworm (Figs 6.19 and 6.20).

- **Tinea**. In ringworm, particularly animal ringworm, the margin of the annular patch is more inflammatory, scaly and raised and there is a tendency for central healing. Scrapings of the skin mounted in potash should reveal hyphae. However, if the peripheral collarette of scale is detected and pityriasis rosea is suspected, the diagnosis may be confirmed when the rest of the eruption develops a few days later.

Truncal eruption

The differential diagnosis of pityriasis rosea (Fig. 6.21) is:

- **Secondary syphilis** (Fig. 6.22)

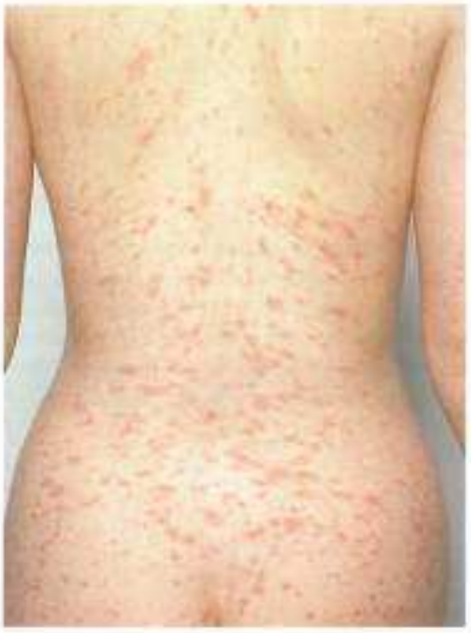


Fig. 6.21 Pityriasis rosea. The rash is usually limited in distribution to the trunk, upper arms and thighs. It is occasionally very itchy and requires treatment with potent topical steroids.

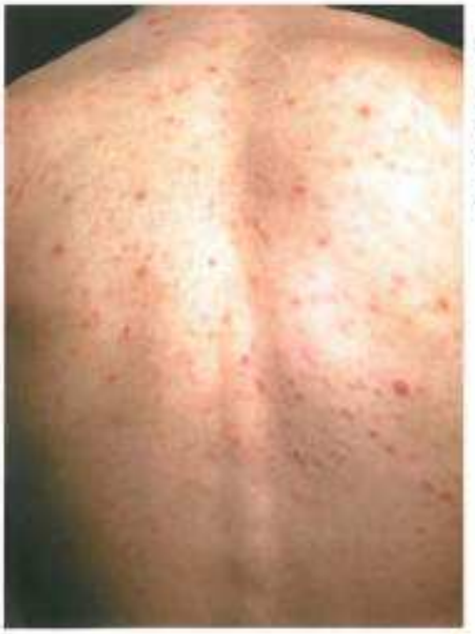


Fig. 6.22 Secondary syphilis. The patient is generally unwell. There is lymphadenopathy and the rash involves the face, genitalia and palms as well as the torso. It does not itch and the serology will be positive.

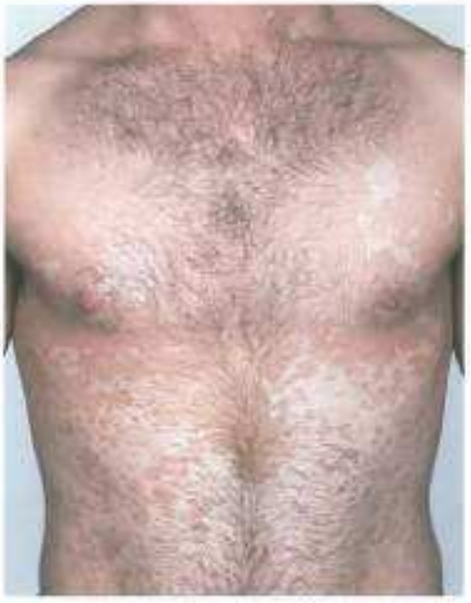


Fig. 6.23 Pityriasis versicolor. The conditions are often confused because of their name. In pityriasis versicolor, the lesions are fawn coloured or off-white and asymmetrical with a tendency to confluence. Both favour the trunk but pityriasis versicolor is slow and insidious in its evolution. Yeasts and pseudohyphae may be found under the microscope in pityriasis versicolor.

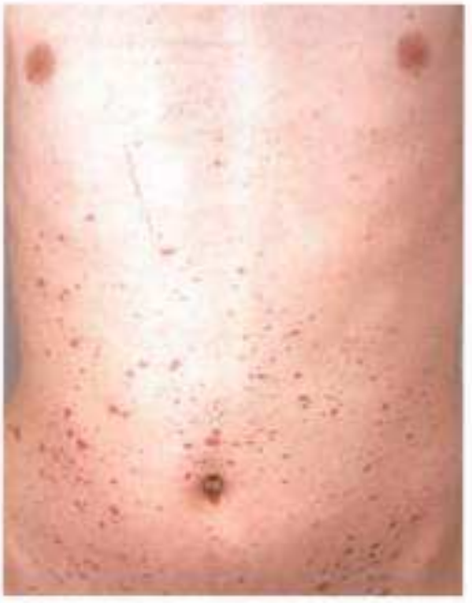


Fig. 6.24 Guttate psoriasis. The onset is explosive with a myriad of small, red papules with a thick, white scale on the torso and limbs 3 weeks after a streptococcal throat infection. Note the line of papules on the right side of his chest secondary to a scratch (Koebner phenomenon).

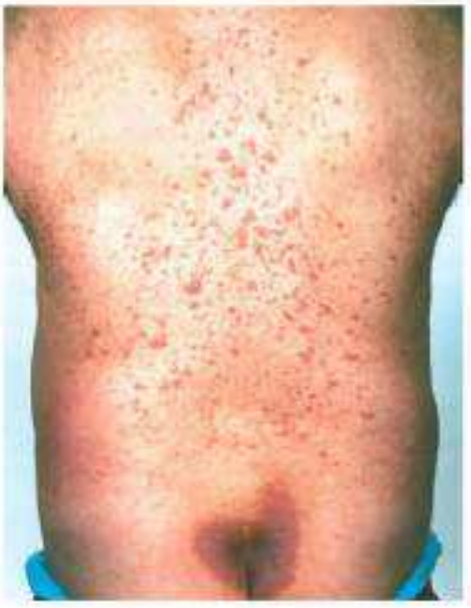


Fig. 6.25 Lichen planus. The eruption is very itchy (unusual for pityriasis rosea) and is composed of discrete purple papules. Pronounced post-inflammatory pigmentation (present at the natal cleft) occurs as the condition heals.

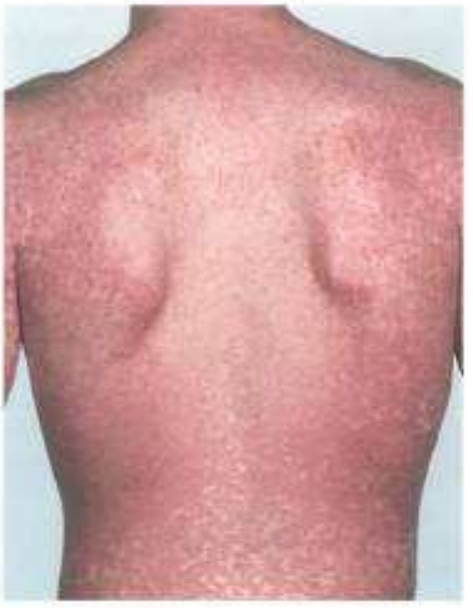


Fig. 6.26 Drug eruption. There are very itchy, morbilliform papules most dramatically seen on the torso. The diagnosis may be missed because the patient had completed the course of amoxicillin prescribed (for a sore throat caused by infectious mononucleosis) when the rash appeared.

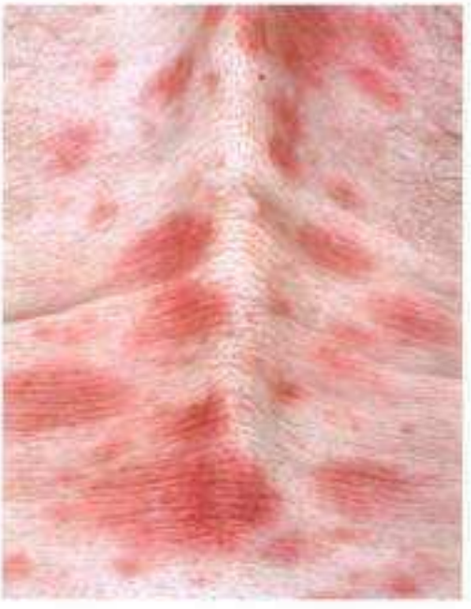


Fig. 6.27 Parapsoriasis. The lesions vary in size and shape. Some are deep red and others pink. Evolution is slow. A biopsy will establish the diagnosis of cutaneous T cell lymphoma.

- **Pityriasis versicolor** (Fig. 6.23)
- **Guttate psoriasis** (Fig. 6.24)
- **Lichen planus** (Fig. 6.25)
- **Drug eruptions** (Fig. 6.26)
- **Parapsoriasis** (Fig. 6.27).

Management

The patient can be told that the eruption will disappear within a few weeks, that it is not infectious and that it is unlikely to recur (2% chance). Also, although it characteristically occurs on the neck, the rash very rarely affects the face. Many patients are asymptomatic but a few suffer severely from itch. Topical steroids do not modify the eruption, but do alleviate the itch. There are unconfirmed reports that erythromycin may abort an attack.

Pityriasis rubra pilaris

A set of rare erythematosquamous disorders of unknown aetiology characterized by lesions that exhibit prominent scaling (pityriasis), perifollicular redness (rubra) and follicular (pilaris) plugging which may become erythrodermic, associated with palmoplantar hyperkeratosis.

Aetiology

It occurs in all races and both sexes. It peaks in the first and fifth decades, giving rise to juvenile and adult types. Griffiths recognizes five subgroups. A sixth associated with HIV infection has been described but it is rather different, with additional features of a filiform pattern of keratoses on the face and upper trunk and often marked acne conglobata.

There is epidermal overactivity, as evidenced by increased labelling indices, and also nail growth, but it is not as fast as in psoriasis. Interest centres around vitamin A metabolism, and decreased levels of retinol-binding protein have been reported in some patients but not confirmed by other investigators. Some patients do respond to retinoids.

Clinical Features

There are five types, with distinct clinical features.

Type I classical adult form

Symptoms

This is an itchy, red and scaly disorder that evolves rapidly and cephalocaudally from the scalp to the whole integument over a few weeks. Half of the patients are affected by this type.

Morphology

The lesions are red or orange (Fig. 6.28) and scaly, ultimately becoming erythrodermic (Fig. 6.29) but with rather striking islands of normal skin (Fig. 6.30). The skin texture is sometimes likened to that of a nutmeg grater. The pilosebaceous follicles are plugged with keratin (Figs 6.31 and

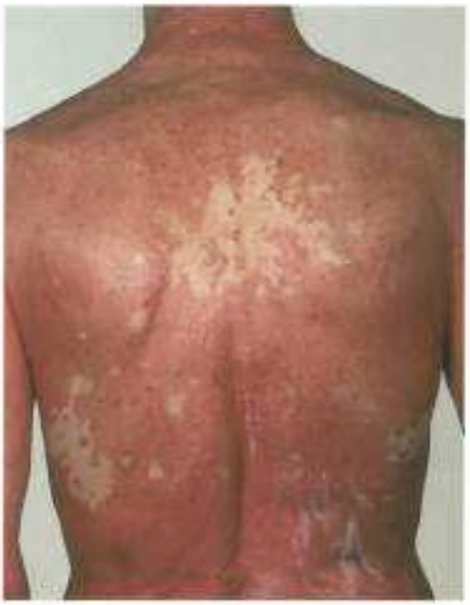


Fig. 6.28 Pityriasis rubra pilaris. The eruption begins on the head and spreads quite abruptly. The islands of normal skin and the strange colour give the clue to this unusual disorder of unknown cause.

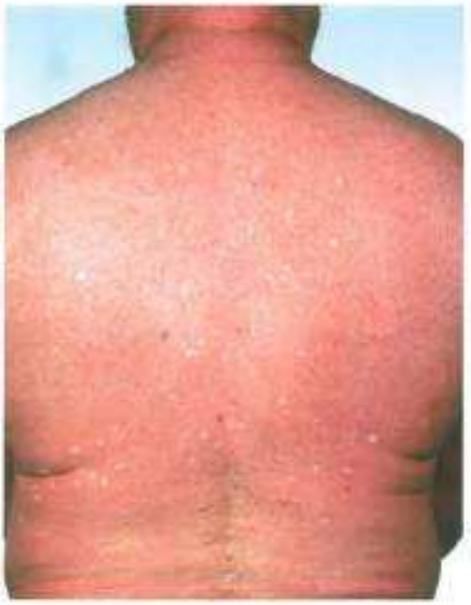


Fig. 6.29 Pityriasis rubra pilaris. The lesions evolve rapidly cephalocaudally; although clearing in some after a couple of years, it may be remarkably persistent in others.

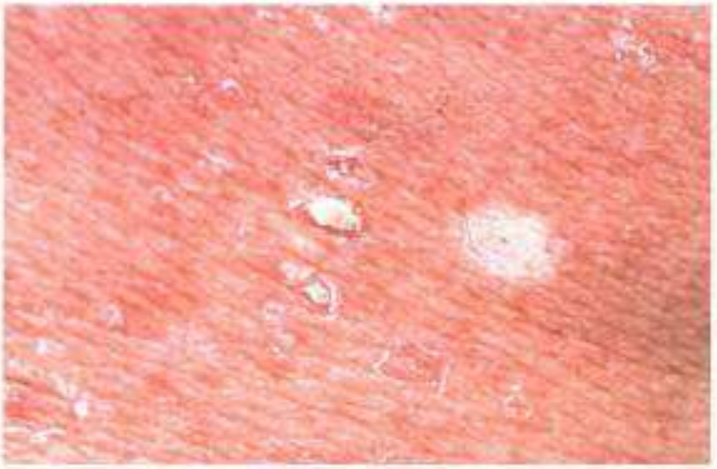


Fig. 6.30 Pityriasis rubra pilaris. This close-up of the patient in Fig. 6.28 shows the coarseness of the scale, the diffuse erythema and a striking characteristic island of normal skin.

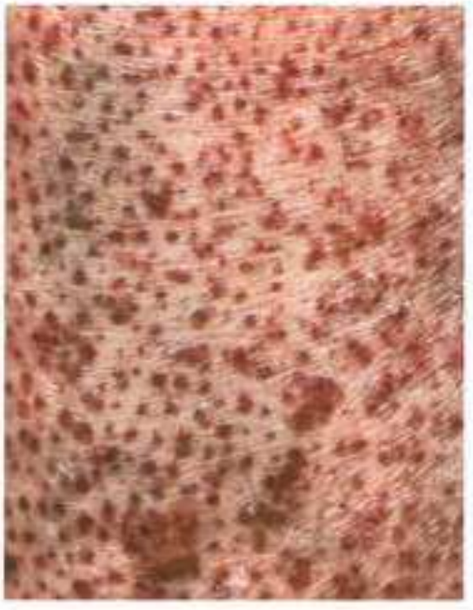


Fig. 6.31 Pityriasis rubra pilaris. The perifollicular erythema and plugging of the pilosebaceous orifices with keratin is the diagnostic clue to the condition.

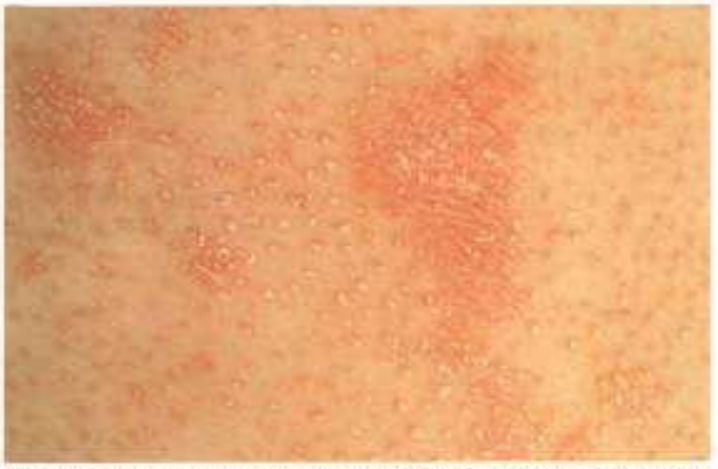


Fig. 6.32 Pityriasis rubra pilaris. Pilosebaceous orifices are plugged with keratin and surrounded by erythema. (By courtesy of the Institute of Dermatology.)

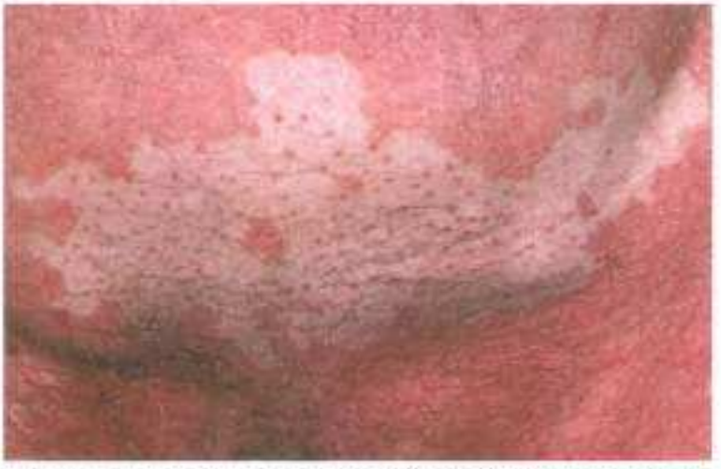


Fig. 6.33 Pityriasis rubra pilaris. There are well-defined small areas of erythema around the hair follicles (hence pilaris) within an area of normal skin surrounded by erythroderma. This is a very characteristic finding.

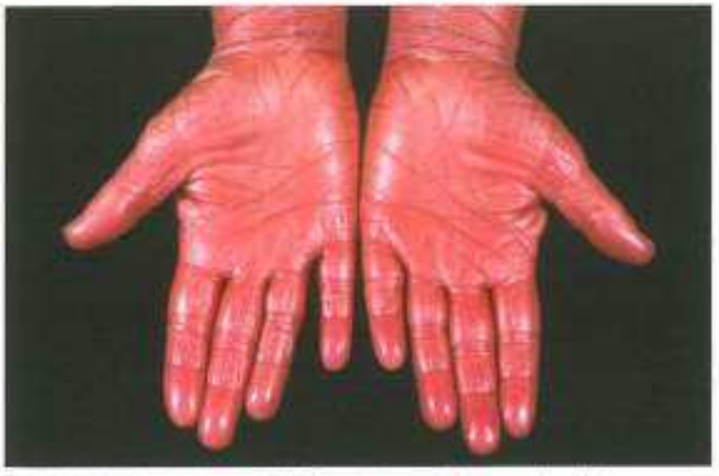


Fig. 6.34 Pityriasis rubra pilaris. The palms and soles are virtually always involved. There may be marked erythema.

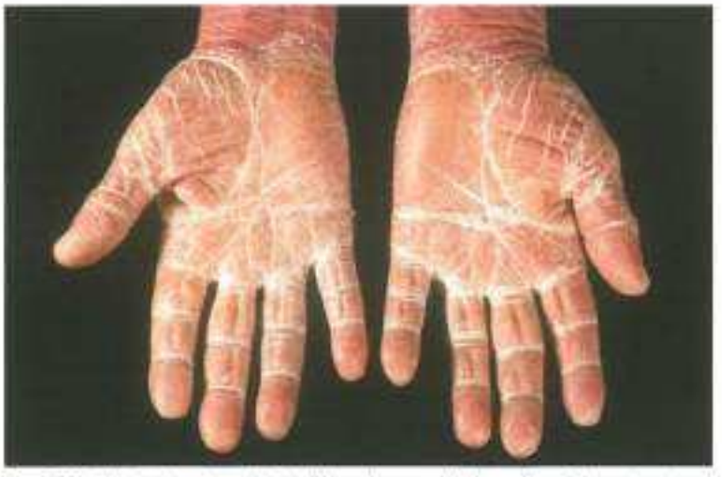


Fig. 6.35 Pityriasis rubra pilaris. The palms may be hyperkeratotic and scaly with a yellowish-orange colour.

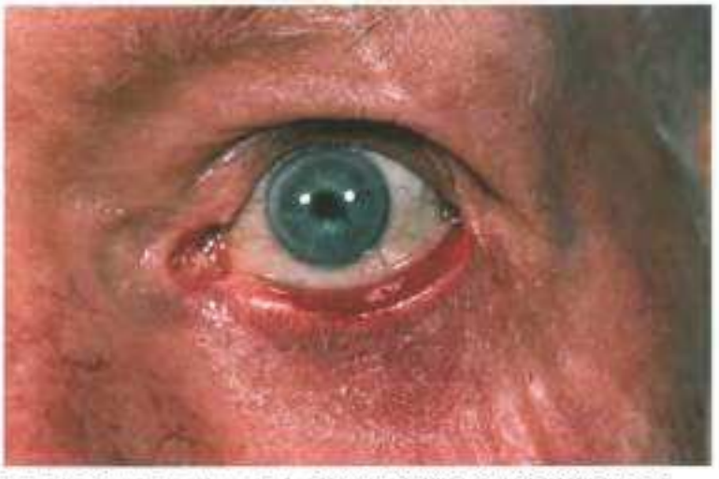


Fig. 6.36 Pityriasis rubra pilaris. The erythroderma results in ectropion, an almost universal finding.

6.32) and surrounded by erythema (Fig. 6.33). The extensor aspects of the fingers, wrists, suprapubic region and thighs are particularly affected in this manner. The erythema (Fig. 6.34) has an orange or yellow hue, especially on the palms (Fig. 6.35) and soles, which are thickened.

Distribution

The cephalocaudal spread is characteristic, but ultimately the whole integument is involved and the patient is erythrodermic, although islands of normal skin are characteristic. Ectropion is striking (Fig. 6.36). The palms and soles are always grossly thickened and yellow in colour. The nails are involved with longitudinal ridges, subungual hyperkeratoses and splinter haemorrhages.

There is usually a spontaneous remission of the type I and III forms within 2 or 3 years, without recurrence.

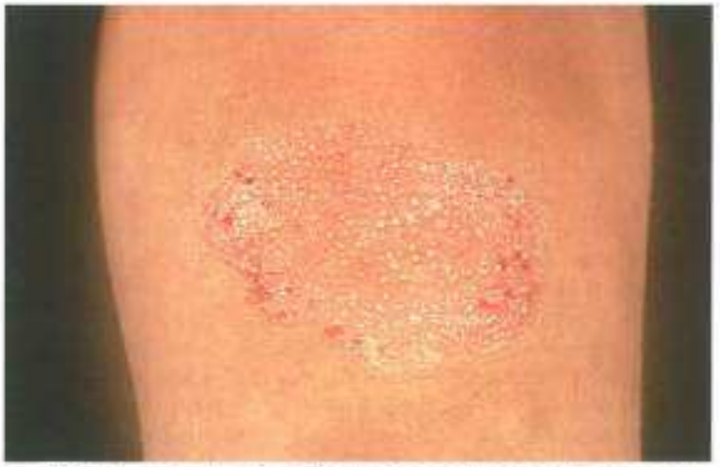


Fig. 6.37 Pityriasis rubra pilaris. The juvenile variant form type (IV) occurs most often on the elbows and knees. It is distinguished from psoriasis by its follicular nature. (By courtesy of Dr A. Griffiths.)

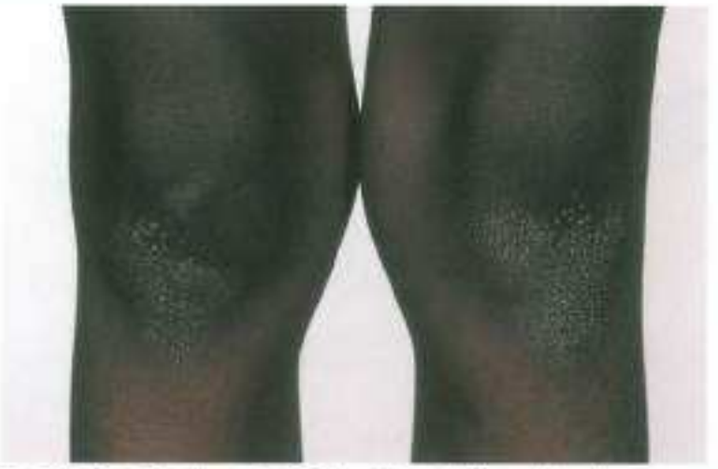


Fig. 6.38 Pityriasis rubra pilaris. The juvenile variant favours the extensor surfaces of the knees and elbows. The plaques are well defined and symmetrical.

Fig. 6.39 Pityriasis rubra pilaris. Close examination of the child in Fig. 6.38 reveals the striking follicular plugging of the lesions within the plaque which serve to distinguish the condition from psoriasis.

Type II atypical adult type

Symptoms

The type II variety is more persistent, lasting many years.

Morphology

The scales are coarse and lamellated and there are suggestions that the type II disorder may be a variant of ichthyosis, although eczematous changes may be present.

Distribution

The legs are particularly involved and palmar plantar hyperkeratosis is present. The hair may be sparse.

Type III classical juvenile form

Symptoms

The onset is more gradual than that of the adult form. It is not present at birth but develops in the latter half of the first decade. About one third of the patients have a positive family history.

Morphology

It shows all the features of adult pityriasis rubra pilaris and may well be a juvenile counterpart. The thickening of the palms and the soles, fine scaling in the scalp, the follicular plugging and the orange red erythema aid the diagnosis.

Distribution

The cephalocaudal spread is characteristic. The eruption usually clears within a couple of years.

Type IV juvenile variant

Symptoms

This is a persistent asymptomatic rash mainly on the knees (Figs 6.37 and 6.38) and elbows; it may involve the scalp, which is almost always mistaken for psoriasis. It occurs in childhood.

Morphology

The eruption is very well defined and the plaques consist of follicular plugging (Fig. 6.39), which serves to distinguish it from psoriasis.

Distribution

Particularly on the knees and elbows. It does not usually progress.

Type V atypical juvenile variant

Symptoms

It presents early in life or even at birth and is chronic.

Morphology

There is erythema and hyperkeratosis, follicular plugging and palmoplantar keratoderma; occasionally sclerodermatous changes may occur in the digits.

Distribution

The eruption is widespread and shows little tendency to clear. Some cases are familial and the condition may represent a form of ichthyosis.

Differential Diagnosis

Apart from the type IV juvenile variant, where the differential diagnosis is psoriasis, the major consideration is other causes of erythroderma, such as drug eruptions, eczema, psoriasis, mycosis fungoides and the Sézary syndrome. These are described elsewhere.

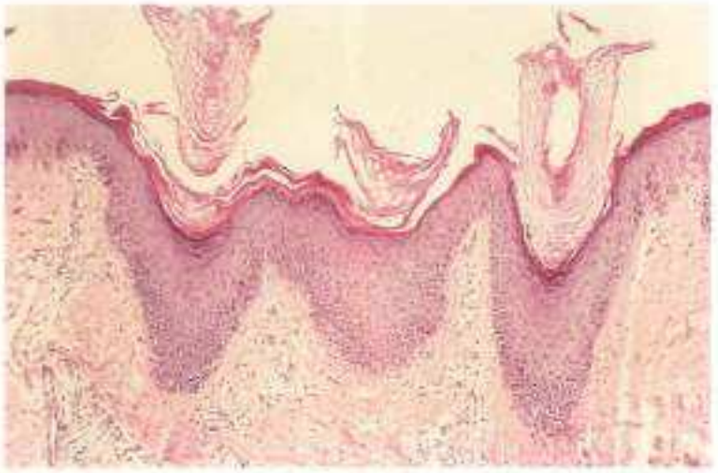


Fig. 6.40 Pityriasis rubra pilaris. The conical keratotic plug is characteristic. A mild chronic inflammatory cell infiltrate surrounds the vessels of the superficial vascular plexus.

Management

It is usually misdiagnosed as psoriasis and the true diagnosis may take time. Observation and repeated biopsies may be necessary. There is a distinctive histology with characteristic hyperkeratotic conical follicular plugging with foci of parakeratosis in the perifollicular shoulder and in the epidermis between the follicles (Fig. 6.40). In other areas a basket-weave hyperkeratosis overlies a more prominent granular cell layer and there is little parakeratosis. There may be mild acanthosis and chronic inflammatory cell infiltrate in the superficial dermis. Laboratory investigations are otherwise unrewarding. The erythrodermic varieties usually require systemic therapy: retinoids (13-cis retinoic acid in fertile females provided contraception is adequate and acitretin for others), methotrexate, ciclosporin and azathioprine have all been tried with variable results. Photochemotherapy may exacerbate the condition but some have found it helpful. Infliximab and adalimumab have been reported to be effective in some patients. The juvenile circumscribed variety is essentially asymptomatic but topical vitamin A may be of benefit. An association with hypothyroidism associated with deletions of chromosome 22q11 has been described in type IV.

Lichen planus and lichenoid eruptions

7

Lichen planus is a common skin disorder. It is named lichen because of a supposed resemblance to the symbiotic plant life of that name, and planus (Latin: flat) because it is characterized by flat-surfaced papules and plaques. There are certain conditions which simulate lichen planus that are termed lichenoid because clinically there are flat-topped shiny papules. Lichenoid eczema and lichenoid drug eruptions are good examples, but lichenoid papules may also occur in lichen striatus and the early lesions of lichen sclerosus et atrophicus. The term lichenoid is also used as a pathological description and refers to any band-like chronic inflammatory cell infiltrate in the papillary dermis that disturbs the interface between the dermis and the epidermis.

Lichen planus

A pruritic mucocutaneous disorder with a distinctive purple papular morphology, characteristic distribution and a specific histology. It lasts a number of months and leaves temporary postinflammatory hyperpigmentation.

Aetiology

Lichen planus affects men and women equally and all races. Nigerians are particularly susceptible. It can present at any time including in childhood but usually is seen between the ages of 30 and 60 years. The cause is unknown but it is associated with various autoimmune disorders such as primary biliary cirrhosis, chronic active hepatitis and diabetes mellitus. It has been described with hepatitis C infection in Italy, the Middle East, South America and Southeastern Asia but this has not been confirmed in the UK, USA or Africa.

Certain drugs, in particular penicillamine (especially when prescribed for primary biliary cirrhosis), arsenic, gold, methyldopa and para-aminosalicylic acid, produce lichenoid eruptions. Antimalarials, such as mepacrine hydrochloride, were responsible for outbreaks of lichen planus in troops during World War II; this eruption had a tendency to be chronic and to produce scarring. Certain drugs can produce a lichenoid photodermatosis, in particular quinine, thiazides (particularly in HIV-positive blacks), streptomycin, isoniazid and demethylchlortetracycline. The pathology is often indistinguishable from lichen planus but the presence of eosinophils may help to distinguish the two and there may be focal parakeratosis.

Histopathology

The pathology is striking. There is an intense infiltration of the epidermis by thymus-derived lymphocytes in a band-like distribution immediately below the epidermis (Fig. 7.1). This pushes the epidermis upwards, forming a papule. The basement membrane and basal cell layer of the epidermis are destroyed by the lymphocytes (Fig. 7.2), which results in liquefaction necrosis of the basal cells. The rete pegs are flattened outwards to give an appearance similar to that of the teeth of a saw. Some of the degenerating epidermal cells stain pink with eosin and are known as colloid bodies. Macrophages in the upper dermis contain pigment lost from the destruction of the lower epidermis. In the epidermis itself there is an increase in the granular cell layer and stratum corneum.

Lymphocytes thus dominate the histology and are almost entirely composed of T-helper/inducer $CD4^+$ lymphocytes (although other investigators have shown a preponderance to $CD8^+$ especially in older lesions). There are increased numbers of Langerhans' cells in the epidermis and dermis in the earliest lesions; these cells are thought to process an antigen, possibly a viral antigen, prior to presentation to the $CD4^+$ T cells, which then have an affinity for the epidermis. This is of interest because lesions identical to lichen planus, clinically, histopathologically and immunologically, occur in the early stages of the graft-versus-host reaction between immunocompetent donor cells and recipient tissues in patients who have undergone bone marrow transplantation or donor lymphocyte infusions.

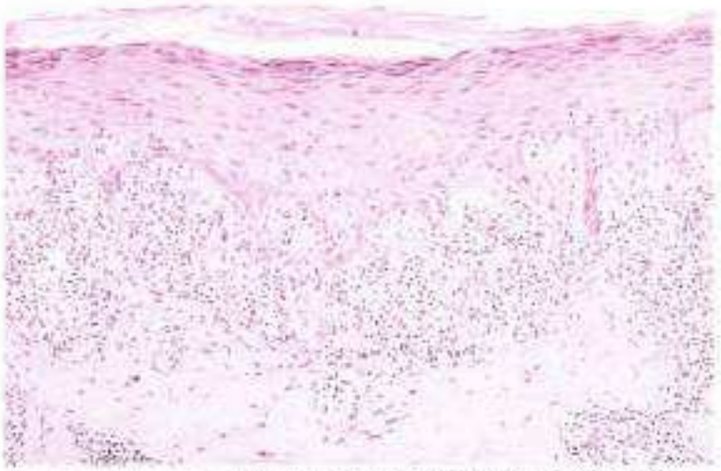


Fig. 7.1 Lichen planus. There is a band of inflammatory cells, predominantly lymphocytes and histiocytes, in the superficial dermis, which destroy the basement membrane and basal cell layer of the epidermis. The epidermis shows irregular saw-tooth acanthosis.

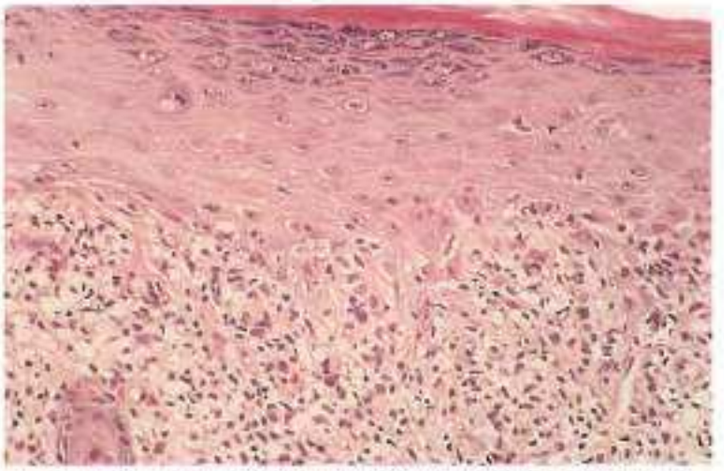


Fig. 7.2 Lichen planus. In this high-power view, hyperkeratosis, prominence of the granular cell layer, acanthosis and hydropic degeneration of the basal layer are present. Scattered, irregular, eosinophilic cytoid bodies are seen in both epidermis and dermis (H&E stain).

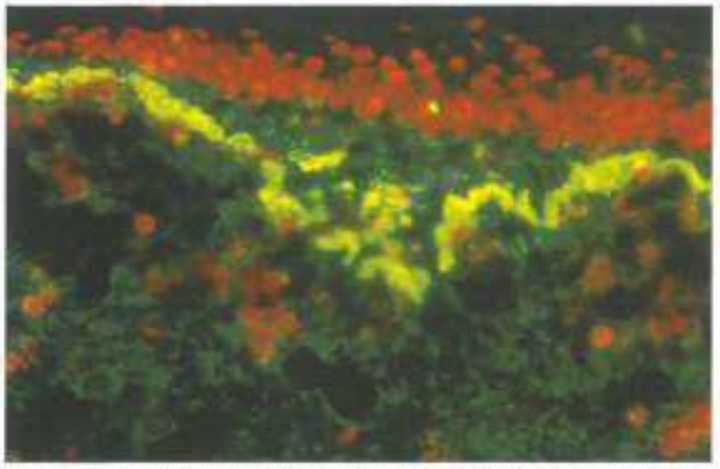


Fig. 7.3 Lichen planus. A brilliant green fluorescence is present in this case due to deposition of fibrin at the basement membrane. (By courtesy of Mr B. Bhogal, Institute of Dermatology.)

Although not specific for lichen planus, the immunofluorescent findings are very suggestive. A broad linear band of fibrin and/or fibrinogen is found at the dermal epidermal junction (Fig. 7.3). The colloid bodies contain IgM (Fig. 7.4), and sometimes other immunoglobulins.

Clinical Features

Symptoms

The eruption begins abruptly and is usually very itchy.

Morphology

The individual lesions are so distinctive and the colour so arresting that the diagnosis may be suspected, almost by examining a single papule. The

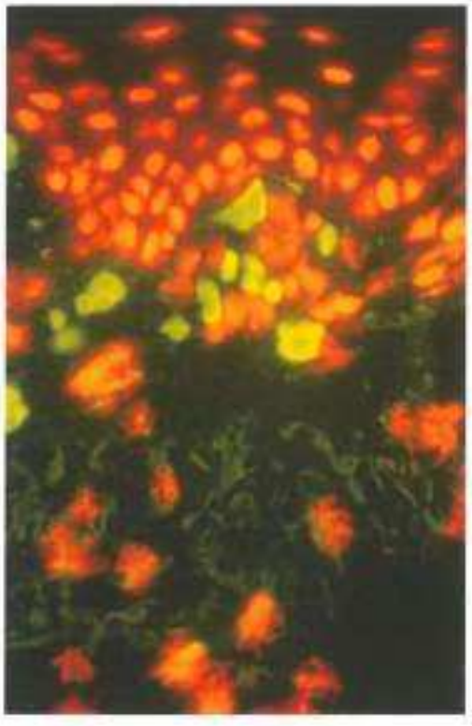


Fig. 7.4 Lichen planus. Cytoid bodies labelled positively (green fluorescence) for IgM. (By courtesy of Mr B. Bhogal, Institute of Dermatology.)

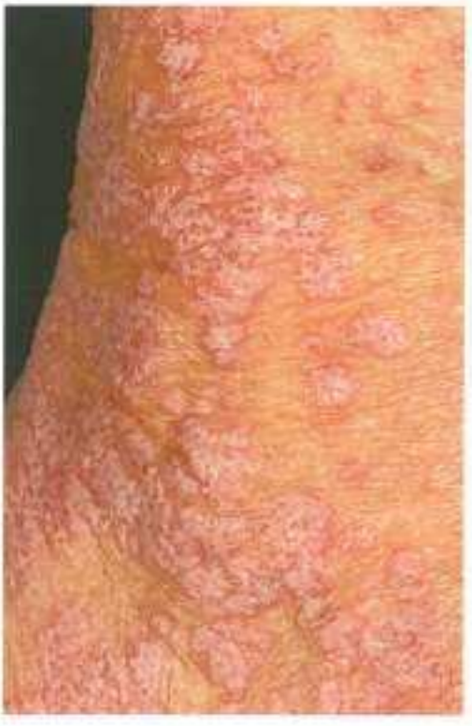


Fig. 7.5 Lichen planus. The purple colour is arresting. Wickham's striae are clearly seen. The backs of the hands are a common site.

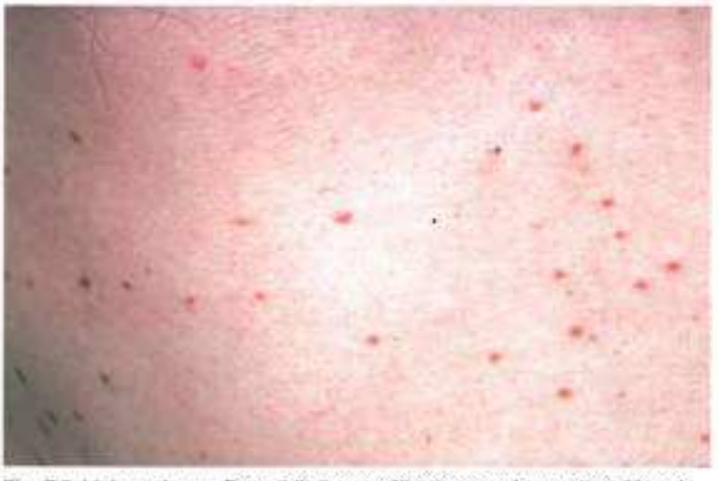


Fig. 7.6 Lichen planus. Essentially the condition is a papular eruption although sometimes (but not here) lesions may become confluent, forming plaques or producing annular or linear arrangements.

Fig. 7.7 Lichen planus. The papules are discrete with a flat-topped shiny surface. The purple colour can be more difficult to discern in a black skin but the Koebner phenomenon may help to clinch the diagnosis.

papule is a mixture of blue and red, and thus purple or 'violaceous' (Fig. 7.5), between 1 and 3 mm in diameter, polygonal in shape and flat topped and shiny when viewed in a good light. Fine, white tracery may be visible on the surface (Wickham's striae: Fig. 7.5). These are believed to be the result of a focal increase in the inflammatory infiltrate and in the thickness of the granular cell layer. The application of mineral oil will highlight these striae. The papules are usually quite discrete (Figs 7.6–7.8) but may become confluent, producing plaques and annular lesions. Linear (Fig. 7.9) and other arrangements (Fig. 7.10) may result from trauma to the skin (Koebner phenomenon). As the lesions heal, postinflammatory hyperpigmentation results (Figs 7.11 and 7.12). This may last a few weeks in a Caucasian, many months in an Asian, and years in a black patient and

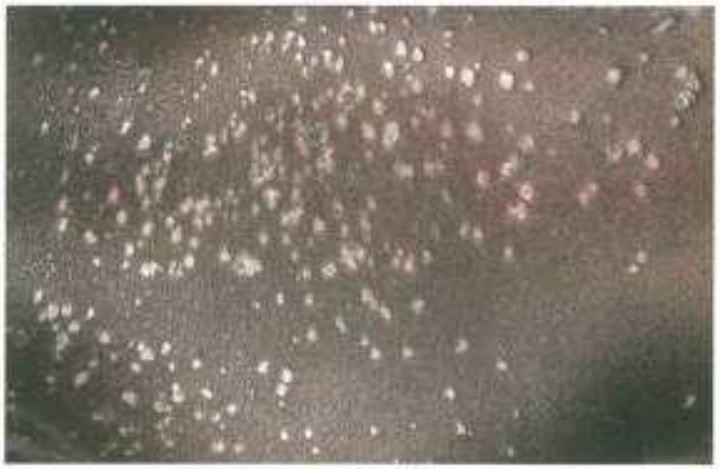


Fig. 7.8 Lichen planus. The flat-topped shiny surface of these polygonal papules are the clue to the diagnosis on the thigh of this Ethiopian.

Fig. 7.9 Lichen planus. Lichen planus is very itchy. The eruption may occur as purple patches in a linear manner secondary to a scratch as part of the Koebner phenomenon.

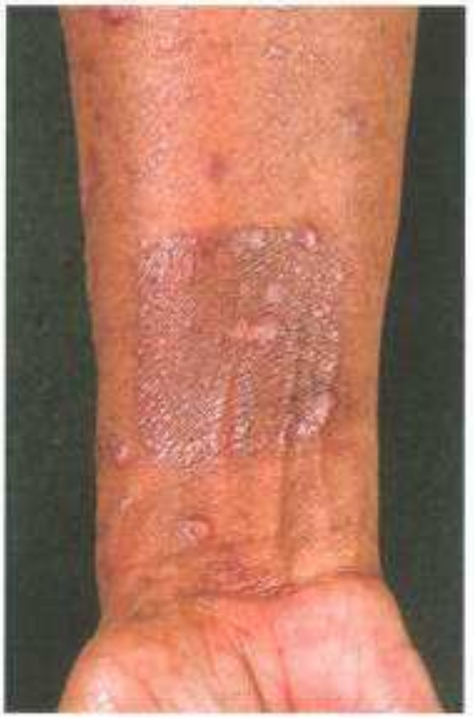


Fig. 7.10 Lichen planus. This patient had burnt her wrist and the Koebner phenomenon occurred. Purple papules and postinflammatory hyperpigmentation are present.

Fig. 7.11 Lichen planus. The initial purple colour of the papules is visible at the edge of this plaque, which has been formed by confluence of the papules. It becomes heavily hyperpigmented in its later stages.

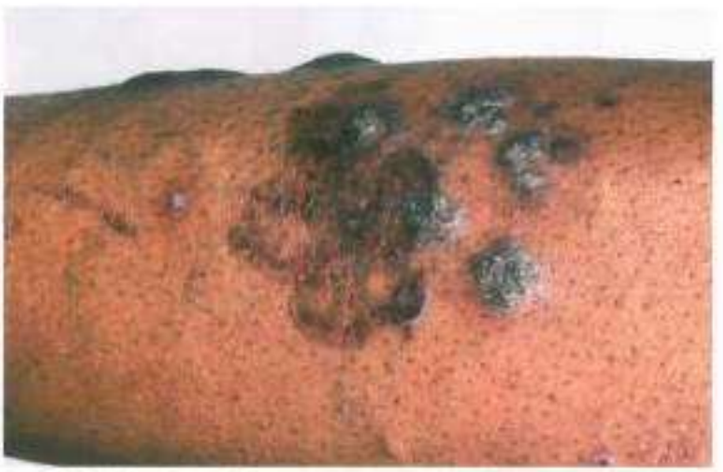


Fig. 7.12 Lichen planus. Three stages are present – a few scattered purple papules, hypertrophic lesions, and prominent postinflammatory pigmentation (centre of picture). The Koebner phenomenon is also visible (left side of picture).

constitutes a very considerable cosmetic problem. Atrophy occasionally occurs as the active lesions resolve (Fig. 7.13).

Distribution

Lichen planus is symmetrical; it has a predilection for the wrists (Figs 7.14 and 7.15), hands, forearms (Figs 7.16 and 7.17), ankles, shins, umbilicus (Fig. 7.18), lumbosacral region and genitalia, although it can occur anywhere. It sometimes only occurs in the axillae and groin (Fig. 7.19) and is known as *lichen planus inversus*. In many the mouth is involved as well, but this is uncommon in blacks. The oral lesions consist of a delicate lace-like white patterning, in streaks or dots, on the inner surface of the cheeks, lips, tongue or gum margins; they are usually asymptomatic.

There is a tendency for fresh lesions to appear over the course of 9–18 months, but ultimately the condition goes into complete remission. Second attacks do occur, but are unusual.

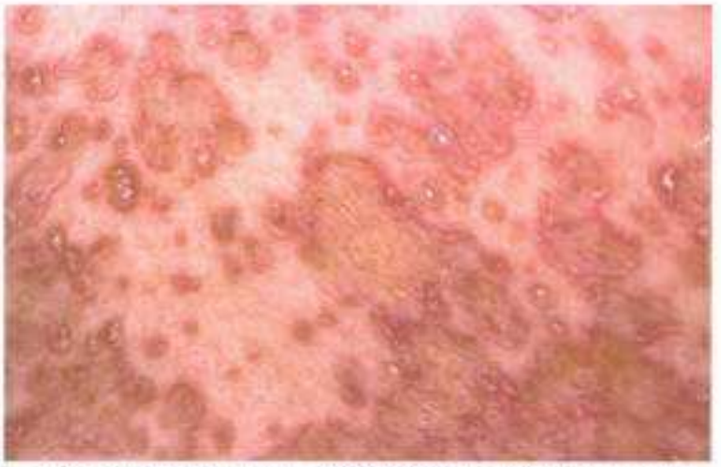


Fig. 7.13 Atrophic lichen planus. Atrophy has occurred within these lesions of lichen planus.

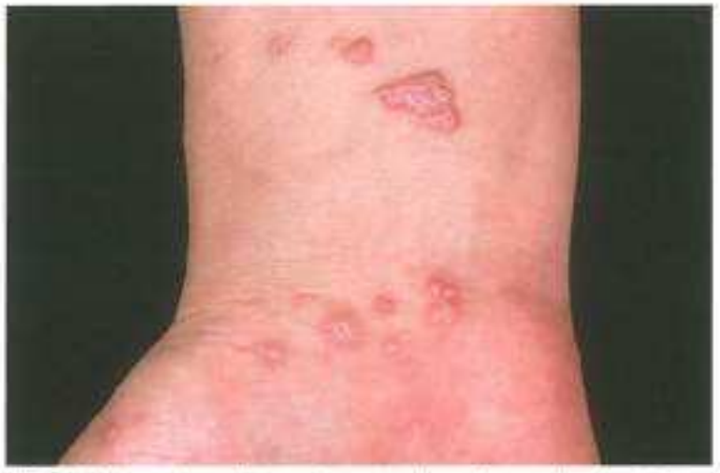


Fig. 7.14 Lichen planus. The papules are purple or violaceous in colour. They are polygonal and flat topped with a shiny fine white tracery on the surface (Wickham's striae).

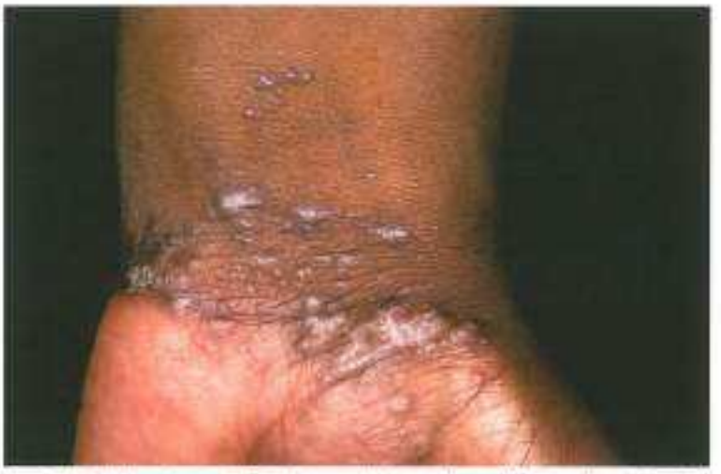


Fig. 7.15 Lichen planus. The flat topped shiny surface of the papules is clearly visible in the black skin even though melanin pigmentation obscures the purple coloration here. The fronts of the wrists are usually involved.

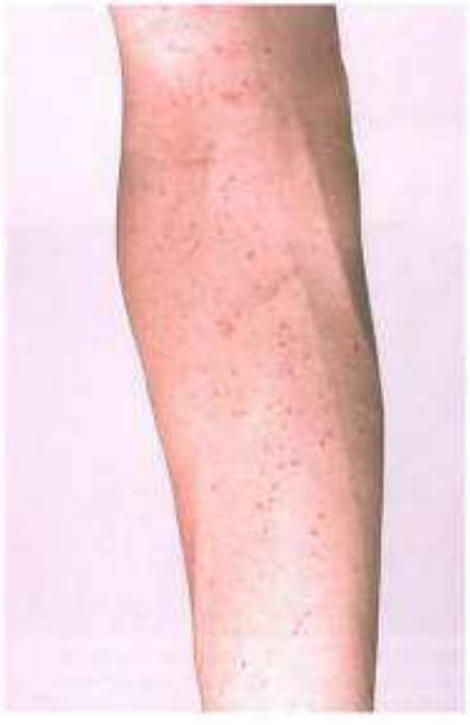


Fig. 7.16 Lichen planus. The forearms are involved. The lesions are discrete and have no surface scale because the pathology is primarily in the upper dermis.

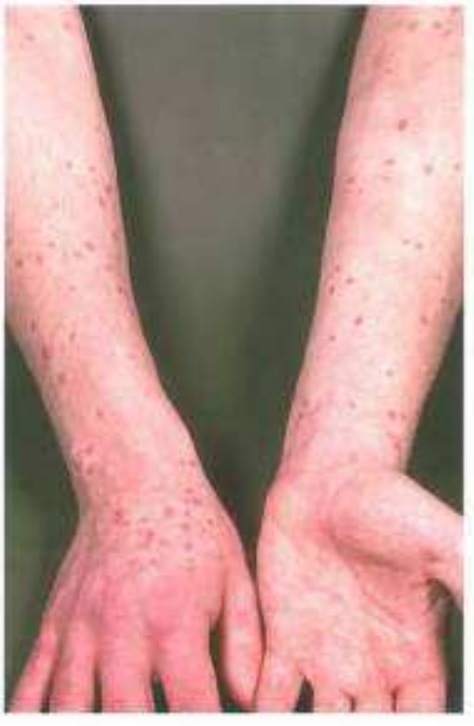


Fig. 7.17 Guttate psoriasis. Guttate psoriasis may be confused with lichen planus because the papules are small and the distribution on the limbs is similar, but it does not itch, the lesions are red and scaly and it erupts explosively 3 weeks after a sore throat.

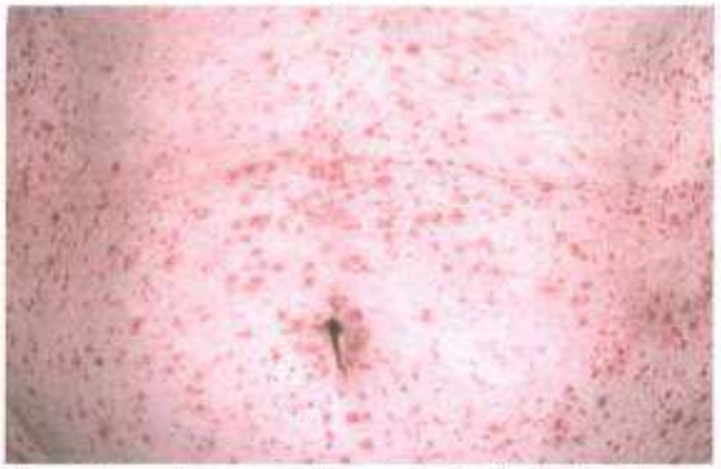


Fig. 7.18 Lichen planus. The papules are usually quite discrete. The itchiness and purple colour would serve to distinguish the eruption from guttate psoriasis.

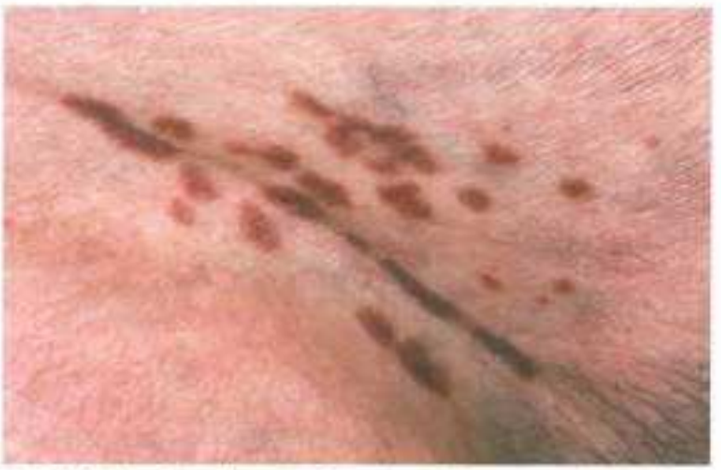


Fig. 7.19 Lichen planus inversus. The groin and axillae are sometimes only involved. The colour of the papules and the linear arrangement of some of them secondary to scratching is characteristic. Biopsy always confirms the diagnosis.

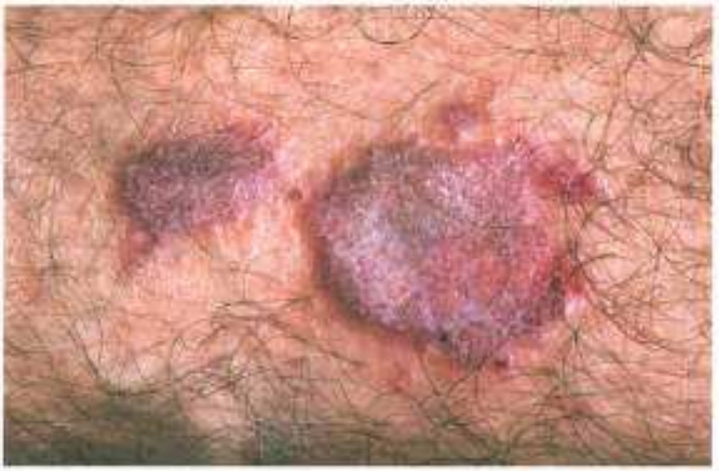


Fig. 7.20 Hypertrophic lichen planus. The lesions are much thicker (hypertrophic) than ordinary lichen planus and have formed plaques. The violaceous colour and Wickham's striae are clearly depicted.

Clinical variants

There are a number of variants of the disease.

- **Hypertrophic lichen planus** Hypertrophic lesions may occur on the shins (Fig. 7.20) during an attack of lichen planus, which then persist despite the disappearance of the rest of the rash. The variant is more common in black patients (Fig. 7.21). The lesions are well-defined, thickened (hypertrophic) plaques. The purple colour (Fig. 7.22) suggests their identity, but a biopsy may be necessary to distinguish it from lichen simplex chronicus although this is usually unilateral. The lesions are difficult to treat, even with intralesional steroids or superpotent steroids under polythene occlusion.

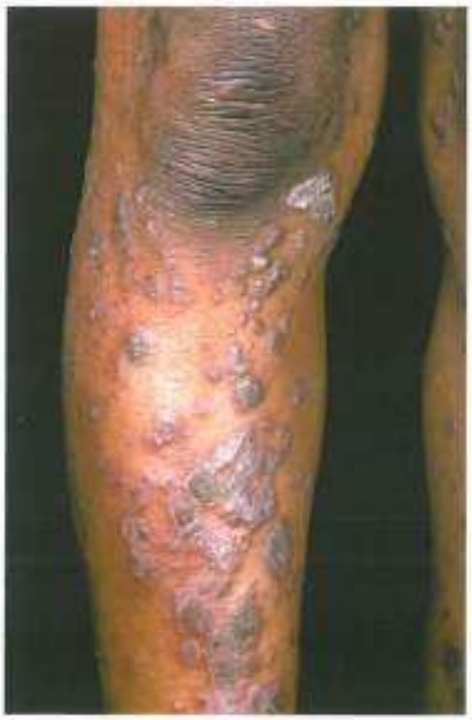


Fig. 7.21 Hypertrophic lichen planus. The hypertrophy is obvious. This variant is more common in black skin. This was an 11-year-old girl. Lichen planus does occur in childhood.

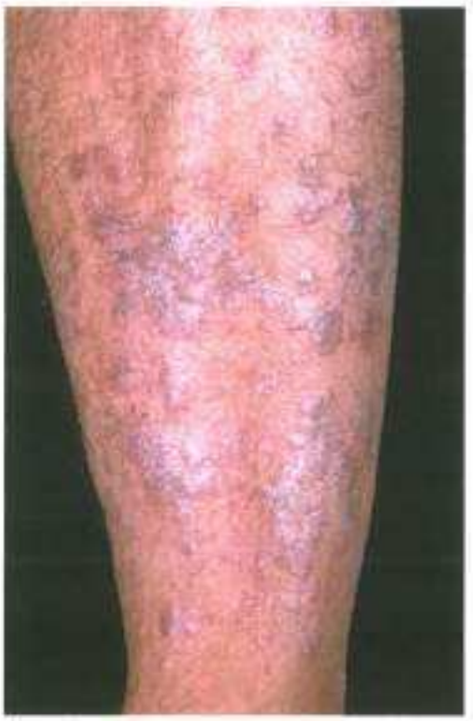


Fig. 7.22 Hypertrophic lichen planus. The lesions are well-defined, thickened hypertrophic plaques. The purple colour may help to distinguish it from lichen simplex chronicus.

- **Annular lichen planus** Although ring-shaped lesions may be a feature of ordinary lichen planus, occasionally there may be just a few scattered asymmetrical circular lesions (Fig. 7.23) on the body, which are often mistaken for ringworm. Careful examination reveals that there is no scaling, and that the margins of the lesion are made up of flat-topped shiny papules with a red/blue hue (Fig. 7.24). Genital lesions are often annular.
- **Palmar or plantar lichen planus** This may occur in isolation (Fig. 7.25) or constitute the major area affected. The diagnosis may be difficult because the thickness of the stratum corneum may obscure the purple colour and the lesions may appear yellow and warty instead (Fig. 7.26).
- **Genital lichen planus** The genitalia are frequently involved along with lesions elsewhere, but occasionally they may be affected on their own or with oral lesions. These consist of individual violaceous shiny, flat-topped papules (Figs 7.27–7.29), often arranged in an annular pattern (Fig. 7.30), with lace-like white streaks (Fig. 7.31) on the surface. Post inflammatory pigmentation may occur, including on the pubis and inner thighs (Fig. 7.32) in either sex. In the female, it is a common cause of pruritus ani (Fig. 7.33) and vulvae.

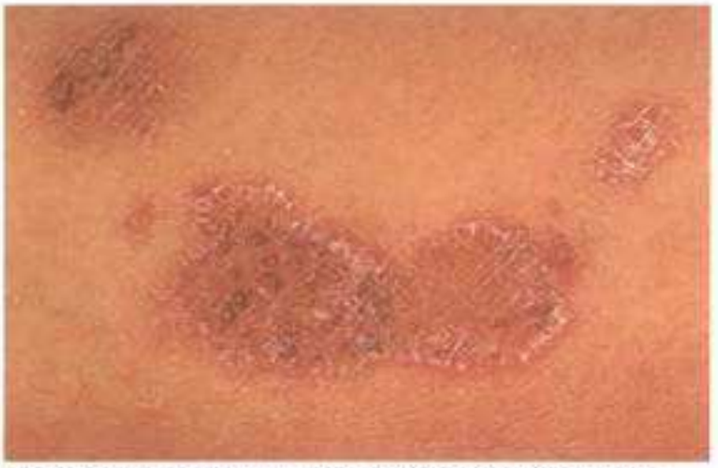


Fig. 7.23 Annular lichen planus. This condition is distinguished by annular configurations. The purple papules at the margin are the clue to diagnosis. Postinflammatory pigmentation has occurred centrally.

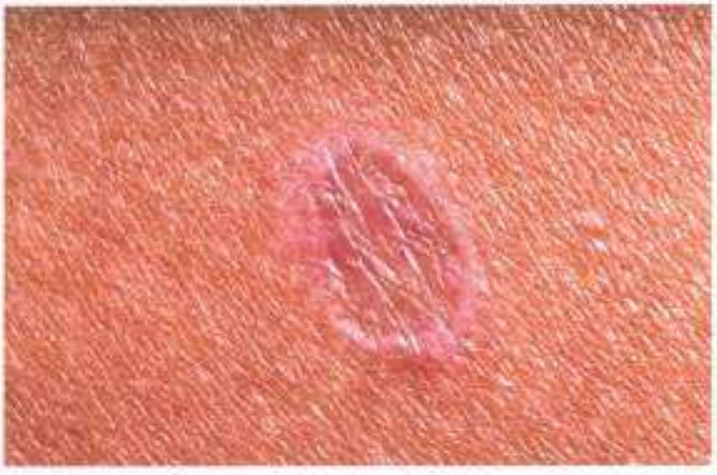


Fig. 7.24 Annular lichen planus. The lesions are usually sparse in annular forms of lichen planus. The purple nature of the papules at the rim are very clear in a Caucasian skin.

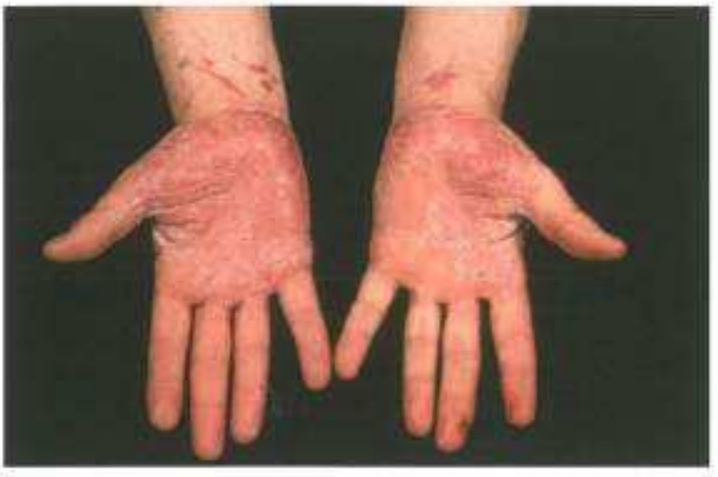


Fig. 7.25 Palmar lichen planus. The usual purple colour may be obscured by the thickness of the stratum corneum in the area. Yellow papules result. Note the Koebnerization at the wrist.

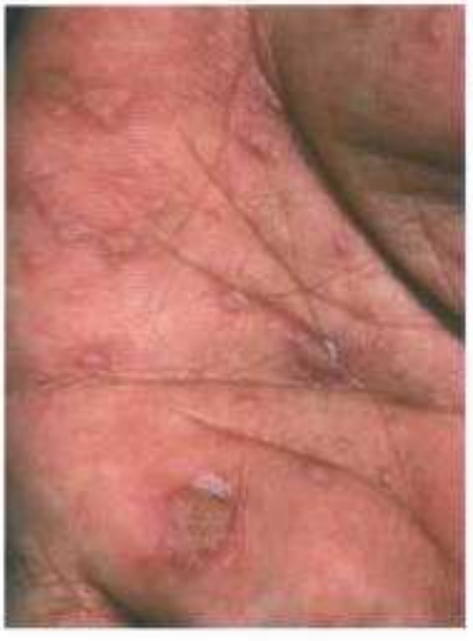


Fig. 7.26 Palmar lichen planus. The diagnosis can be difficult when only the palms are involved. Biopsy is invaluable but the diagnosis would be suspected because the lesions are purple and Wickham's striae are present.

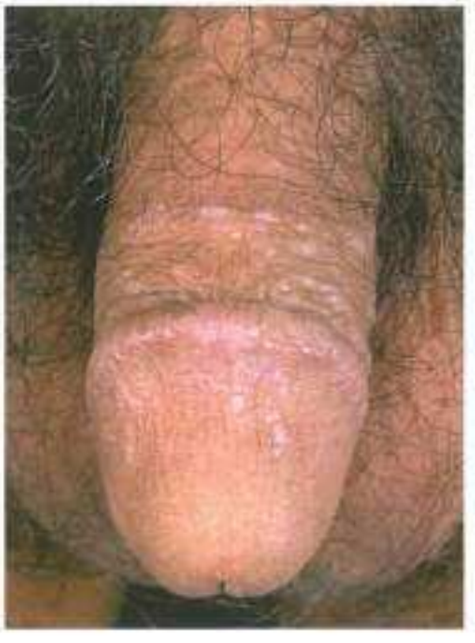


Fig. 7.27 Genital lichen planus. Purple shiny papules are present on the glans and shaft of the penis. Occasionally the genitalia and mouth are the only sites involved.

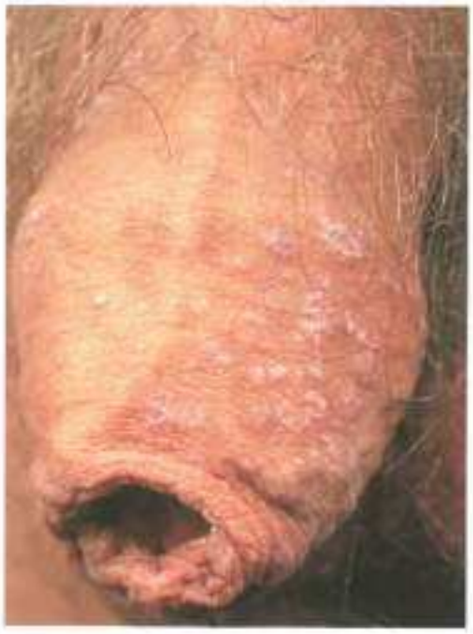


Fig. 7.28 Lichen planus. There are flat-topped, purple papules with white striae on the shiny surface. There are usually lesions in the mouth if not elsewhere.

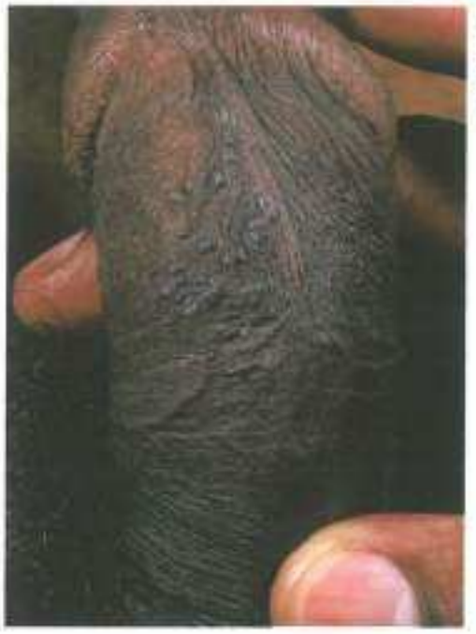


Fig. 7.29 Genital lichen planus. The discrete nature of the papules is evident. They are often mistaken for viral warts.

Fig. 7.30 Genital lichen planus. Annular arrangements are common in this area. Note the purple colour and shiny surface.

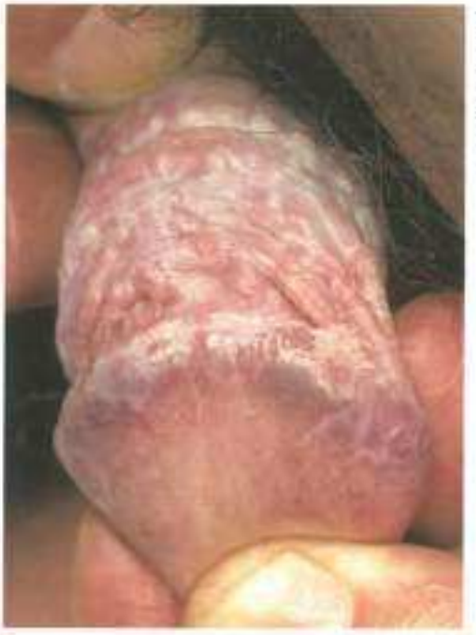


Fig. 7.31 Lichen planus. A reticulate (net-like) white pattern may occur on the genitalia similar to that found on the buccal mucosa in lichen planus.

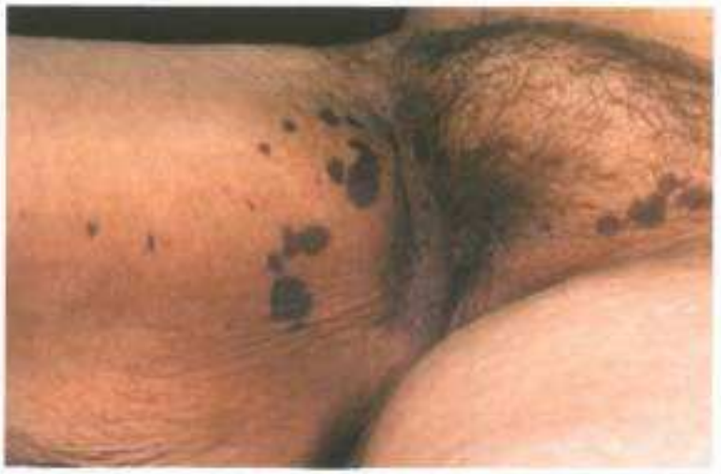


Fig. 7.32 Lichen planus. Postinflammatory pigmentation, which may be marked, is the usual consequence of lichen planus, which regularly affects the groin and genitalia.

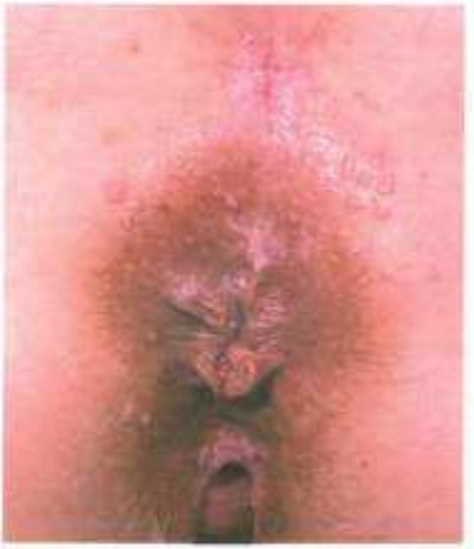


Fig. 7.33 Perianal and vulval lichen planus. Lichen planus is a common cause of pruritus ani and vulvae. The purple papules and postinflammatory pigmentation are evident and superpotent steroids provide relief.

Fig. 7.34 Genital lichen planus. In addition to purple papules, a lace-like white reticular patterning is visible, similar to the changes often seen in the mouth in lichen planus.

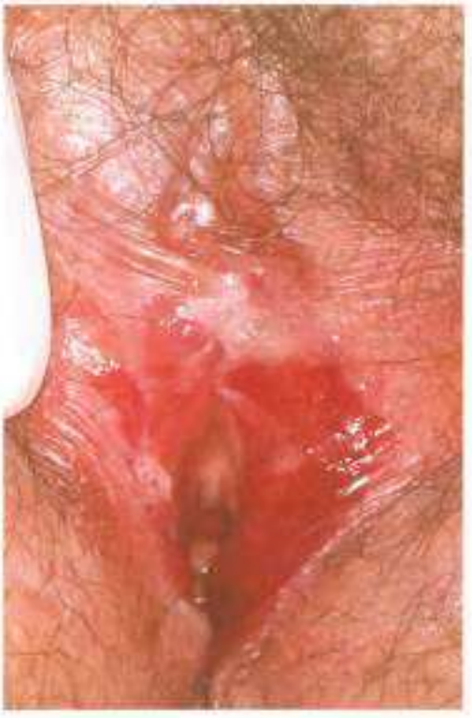


Fig. 7.35 The vulvovaginal-gingival syndrome. This is an erosive disorder of the vulva and vagina associated with a desquamative gingivitis (Fig. 7.36). The histology is diagnostic and it responds to potent topical steroids. (Courtesy of Dr Sallo Neill.)

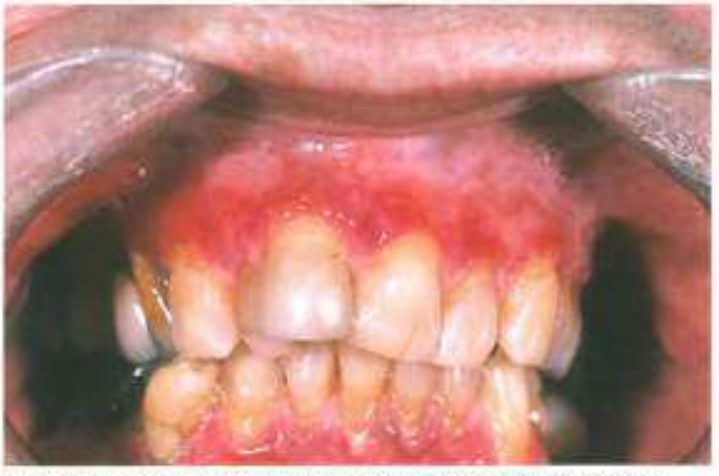


Fig. 7.36 The vulvovaginal-gingival syndrome. An erosive desquamative gingivitis is associated with the genital disorder.

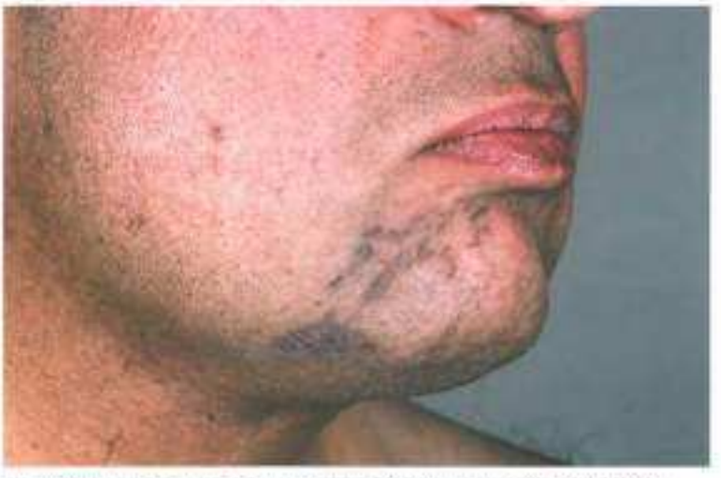


Fig. 7.37 Lichen planus pigmentosus. This is an uncommon variant, seen primarily in Indians, often affecting sun-exposed or intertriginous areas. Pigmentation is predominant and it may be reticulate.

- **The *vulvovaginal-gingival syndrome*** This describes a variant of classical vulval lichen planus (Fig.7.34) with erosions of the vulva and the vestibule of the vagina (Fig. 7.35) associated with a desquamative gingivitis in the mouth (Fig. 7.36). It is often misdiagnosed, but a biopsy should establish the true diagnosis, which is important because it responds to superpotent steroids.
- **Lichen planus pigmentosus** This condition is well recognized in Indians. It is most common in a photo-distribution (Fig. 7.37) or inverse intertriginous site. There is no preceding inflammation. It probably represents postinflammatory dermal pigmentation secondary to damage to the dermo-epidermal junction by lichen planus or a lichenoid reaction.
- **Acute generalized lichen planus** This is a rare exanthematic form of lichen planus with a sudden onset and involvement of most of the cutaneous surface (Fig. 7.38). Initially the eruption is red but becomes purple as it progresses. Scrutiny of the individual lesions reveals the shiny, flat-topped papules.

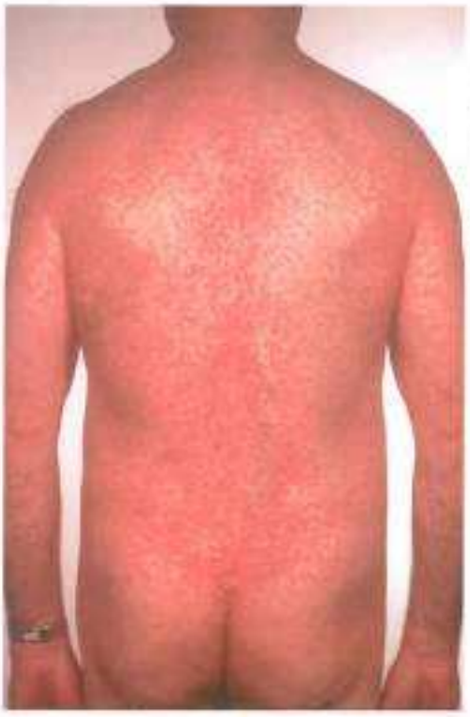


Fig. 7.38 Acute generalized lichen planus. Rarely lichen planus erupts as an exanthem. Close inspection of the individual papules will suggest the diagnosis and biopsy will confirm it. Systemic steroids may be necessary.

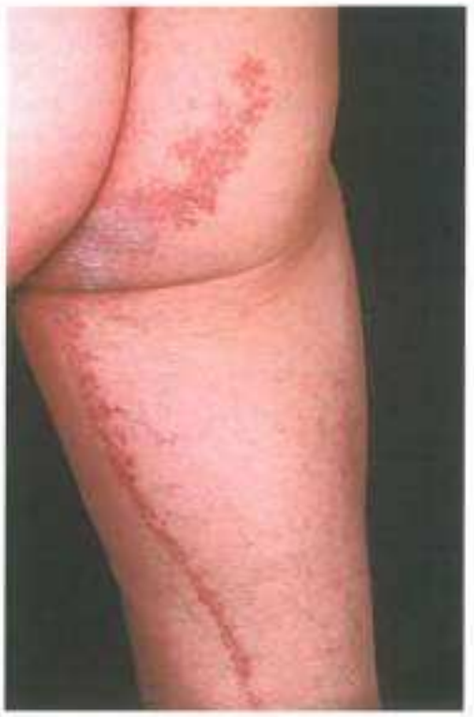


Fig. 7.39 Linear lichen planus. This is uncommon. The papules are purple and lichenoid and occur in a linear distribution. A biopsy will distinguish it from lichen striatus.

Fig. 7.40 Lichen planopilaris. Follicular papules that are purple, pigmented and flat topped are present. Biopsy may be required to establish the diagnosis.

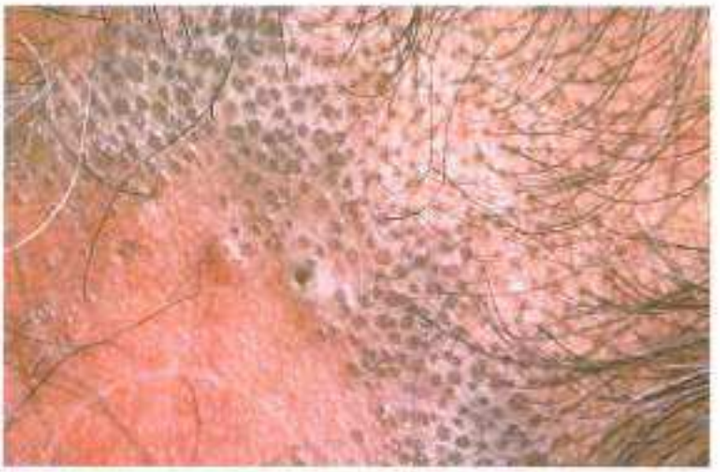


Fig. 7.41 Lichen planopilaris. Lichen planus that predominantly involves the hair follicles may result in scarring alopecia. (By courtesy of the Institute of Dermatology.)

- **Linear lichen planus** This is rare. The individual morphology is that of lichen planus but the distribution is zosteriform (Fig. 7.39) although not corresponding to a dermatome but within Blaschko's lines. It is often seen in childhood and may be followed by ordinary lichen planus later.
- **Lichen planopilaris** (see Ch. 26) In this variant the lesions occur predominantly around the hair follicles (Fig. 7.40). If this occurs in the scalp (Fig. 7.41), the inflammatory infiltrate extends deeply around the hair follicle, ultimately destroying it and resulting in scarring and permanent hair loss (Fig. 7.42) unless systemic steroids are given early in the course of treatment. Typical cutaneous or mucosal lesions may also be present.

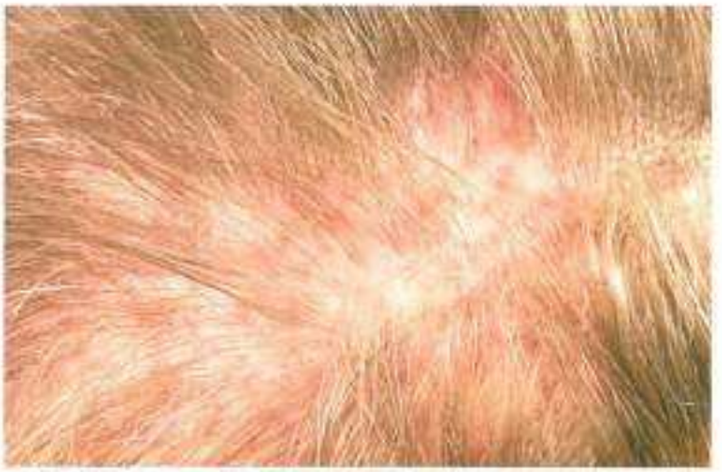


Fig. 7.42 Lichen planopilaris. Scarring alopecia. Lichen planus occurs rarely in the scalp; if it does, scarring may result.

- **Actinic lichen planus** Ultraviolet light irradiation may traumatize lichen planus and induce a Koebner phenomenon in exposed sites (Fig. 7.43). It may occur in a localized manner on an exposed site (Fig 7.44).
- **Lichen planus subtropicus** There is also an actinic variety, which seems to be a separate entity (syn. *Lichen planus subtropicus*) and is seen in the Mediterranean, Indian subcontinent and Middle East, particularly in children. The lesions are often annular (Fig. 7.45) with a striking hyperpigmentation and surrounding hypopigmentation (Fig. 7.46). They occur on exposed areas, particularly the face and neck.
- **Bullous lichen planus** Pathologically vacuolar degeneration results from damage to the basement membrane by the lymphohistiocytic infiltrate (known as Max–Josephs spaces). Clinically, subepidermal blisters may be formed, particularly on the lower legs (Figs 7.47 and 7.48).

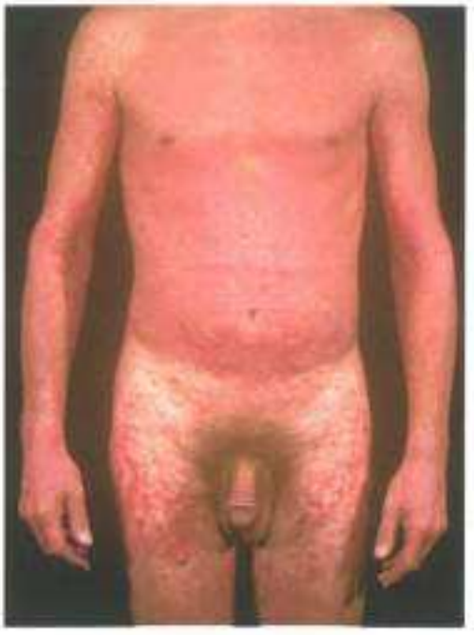


Fig. 7.43 Actinic lichen planus. Lichen planus has occurred on sunburnt skin. The purple colour is well illustrated. (By courtesy of the Institute of Dermatology.)

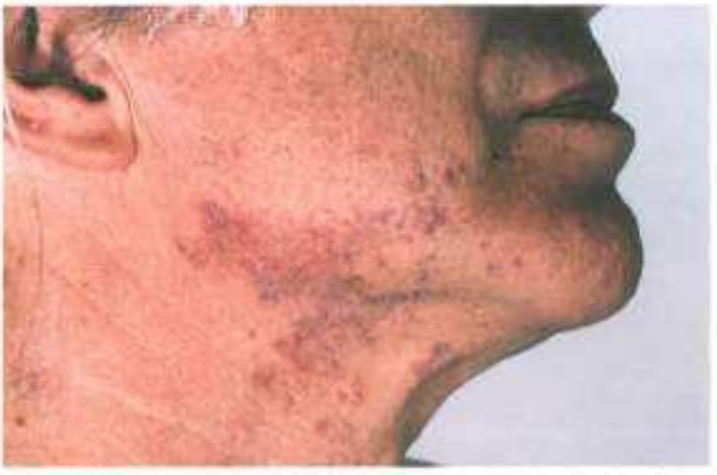


Fig. 7.44 Actinic lichen planus. This is an uncommon phototoxic variant of lichen planus. There are purple papules but it was the biopsy which established the diagnosis.

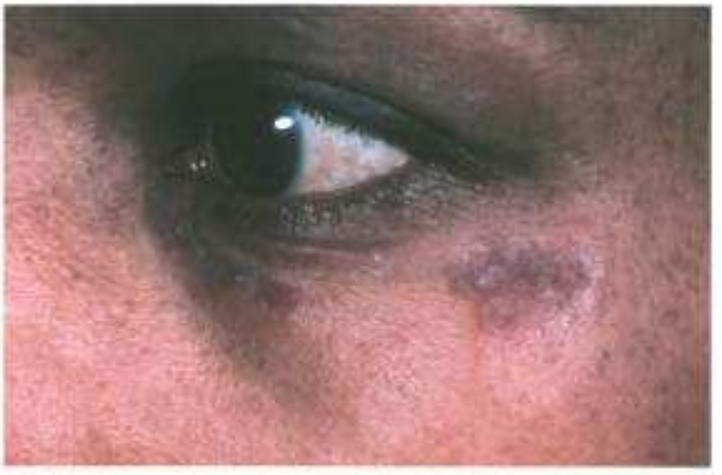


Fig. 7.45 Lichen planus subtropicus. The lesions are often sparse and annular and confined to the face. Pigmentation predominates here but the purple margin aids diagnosis. Indians are prone to this actinic variety.

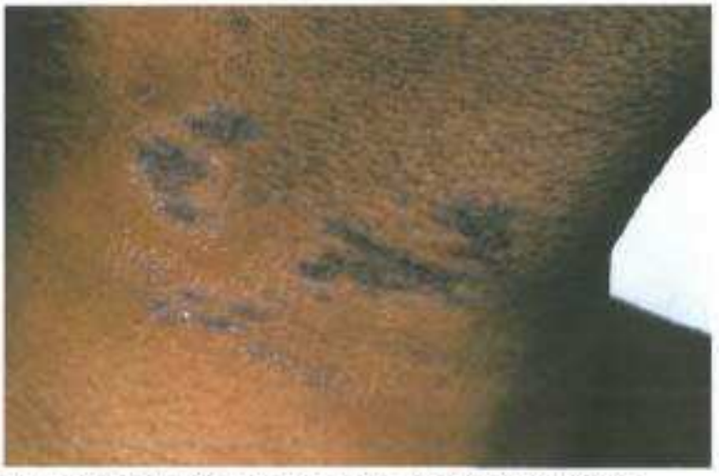


Fig. 7.46 Actinic (subtropic) lichen planus. The lesions have a deeply pigmented centre surrounded by shiny papules. It occurs on exposed skin (usually face and neck) in those from the Middle East and India.

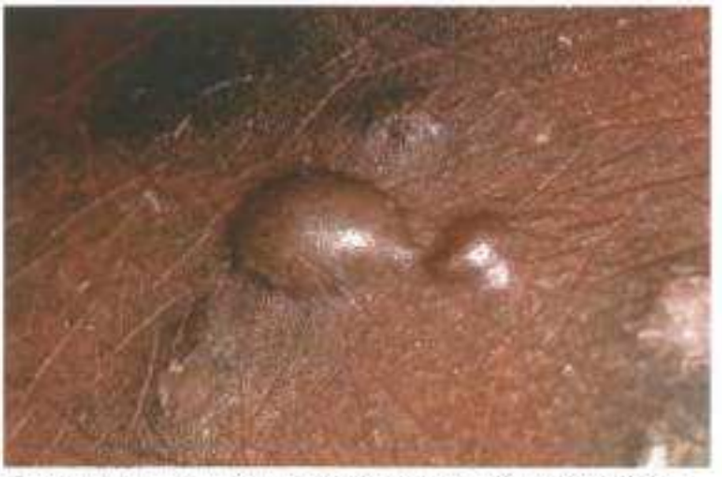


Fig. 7.47 Bullous lichen planus. Blisters may occur in the course of ordinary lichen planus from intense damage to the basement membrane, particularly on the lower legs.

- **Lichen planus pemphigoides** This is an acute and generalized lichen planus that is associated with large tense blisters appearing both on normal skin and on skin affected by lichen planus. Direct immunofluorescence shows deposition of IgG and complement C3 in a linear configuration along the basement membrane (Fig. 7.49). A 180 kDa antigen has been found that is similar to that of bullous pemphigoid and it does seem as if this condition is in fact two separate diseases, lichen planus and bullous pemphigoid. It may be that cytotoxic damage to basal cells in lichen planus unmasks or makes new antigens which lead to antibody formation and induction of bullous pemphigoid. Drugs such as cinnarizine, captopril, ramipril, simvastatin and lisinopril may induce a similar picture. Most patients respond readily to local superpotent or systemic steroids.
- **Lichen nitidus** This is a distinctive condition. It is seen most frequently in young blacks. The morphology of the lesion is rather like a minute pinhead (Fig. 7.50) version of ordinary lichen planus although it is flesh coloured (Fig. 7.51) and not purple. It particularly affects the penis, inner forearms, wrists and lower abdomen. Both lichen planus and lichen nitidus may coexist, but some believe that lichen nitidus is a separate entity because it is chronic, does not itch and responds poorly

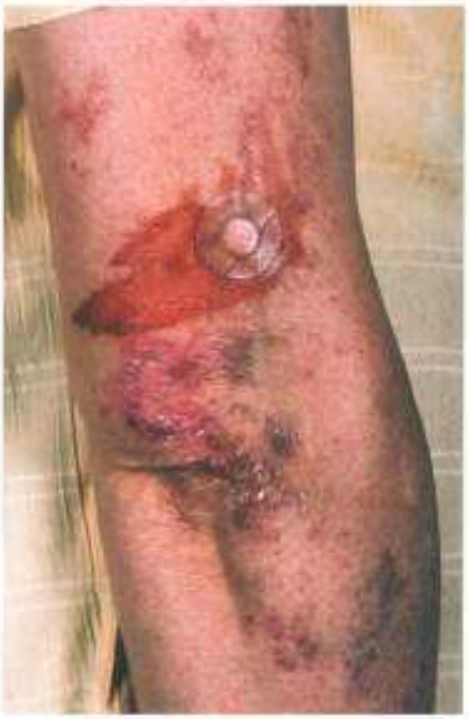


Fig. 7.48 Bullous lichen planus. Blisters and erosions may occur in the course of ordinary lichen planus from intense damage to the basement membrane, particularly on the lower legs.

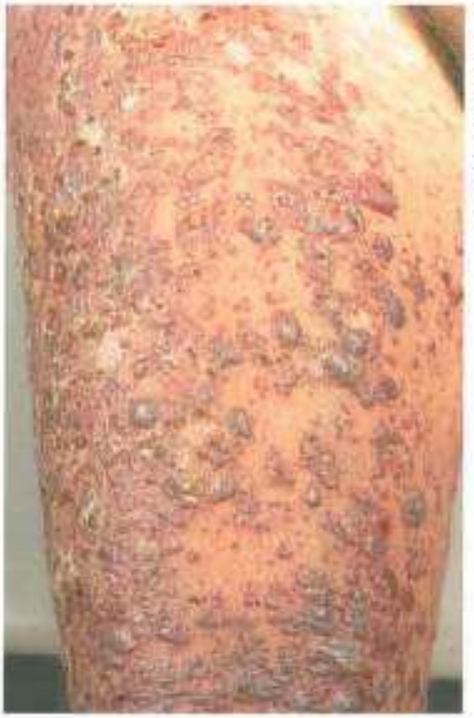


Fig. 7.49 Lichen planus pemphigoides. This is an acute generalized lichen planus associated with blistering and deposition of IgG and C3 along the basement membrane. (Courtesy of Dr A. C. Pembroke.)

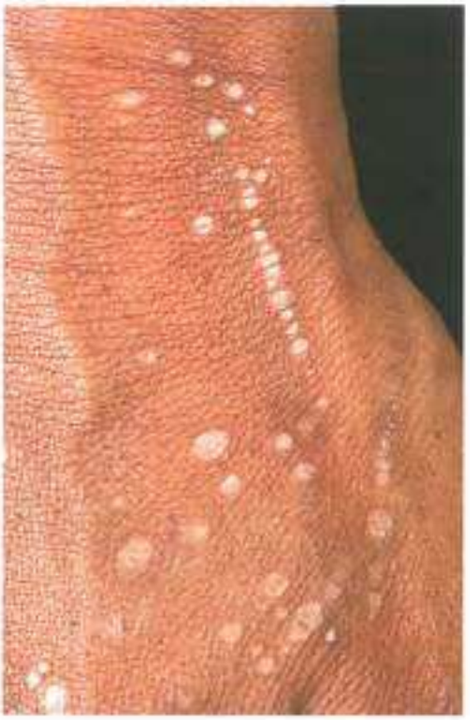


Fig. 7.50 Lichen nitidus. The condition clinically is a miniature version of lichen planus but it does not necessarily itch or respond well to therapy. The Koebner phenomenon is obvious.

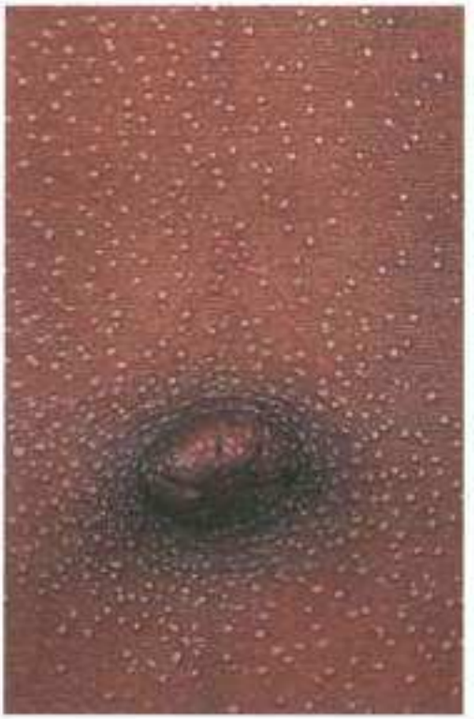


Fig. 7.51 Lichen nitidus. There are a myriad of tiny, shiny flesh-coloured or hypopigmented papules on the abdomen centred around the umbilicus.

to treatment. Nevertheless, the histology is similar (Fig. 7.52), although it may become granulomatous in older lesions and was originally, therefore, believed to be a tuberculid. The immunofluorescence studies are negative for immunoglobulins at the dermal–epidermal interface, unlike lichen planus.

- **Nail involvement** In a minority of patients, there is slight thinning of the nail plate, which grows forward from the cuticle giving the appearance of longitudinal lines or depressions in the nail plate (Fig. 7.53). The fingers are involved more frequently than the toes and usually only two or three nails are affected, although all of them may be affected eventually. Occasionally, however, severe damage occurs to the nails, leading to an adhesion between the epidermis of the dorsal nailfolds and the nailbed, causing partial destruction of the nail, a change known as pterygium formation (Fig. 7.54).

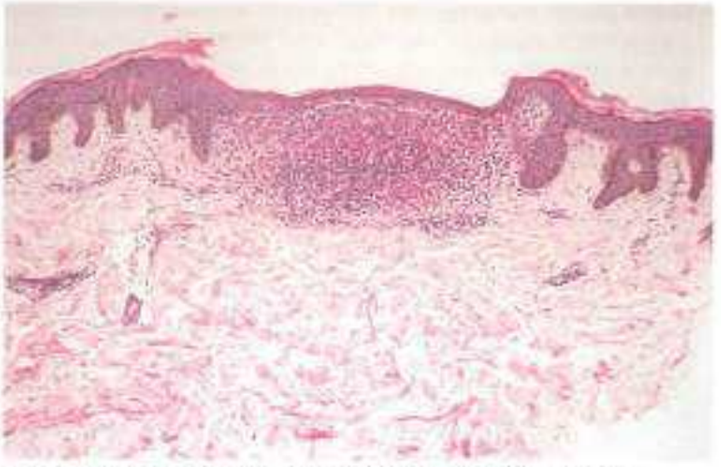


Fig. 7.52 Lichen nitidus. There is a small papule bordered by angulated epidermal rete ridges or pegs.

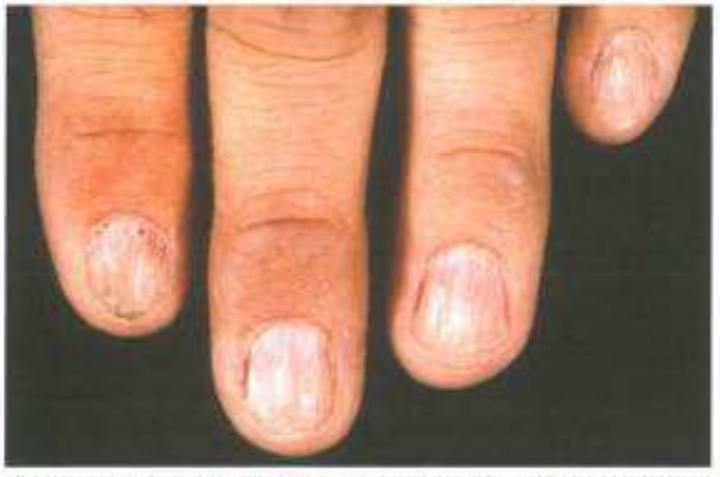


Fig. 7.53 Lichen planus of the nails. Longitudinal lines sometimes occur in the nail plates with lichen planus. (By courtesy of the Institute of Dermatology.)

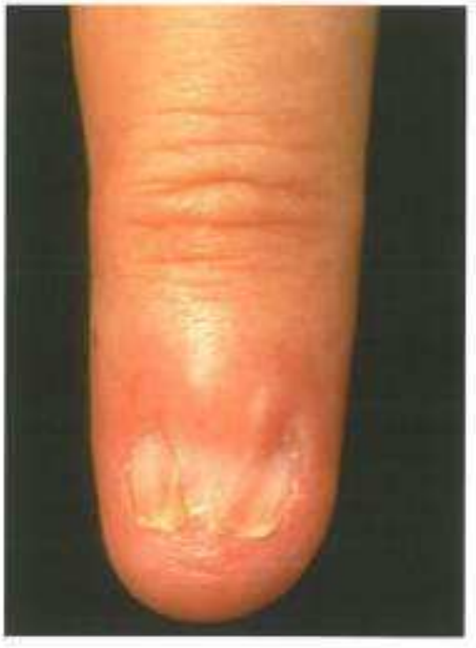


Fig. 7.54 Lichen planus of the nails. Adhesions may form between the epidermis of the posterior nailfold and the nail plate. The result is known as pterygium formation. (By courtesy of the Institute of Dermatology.)

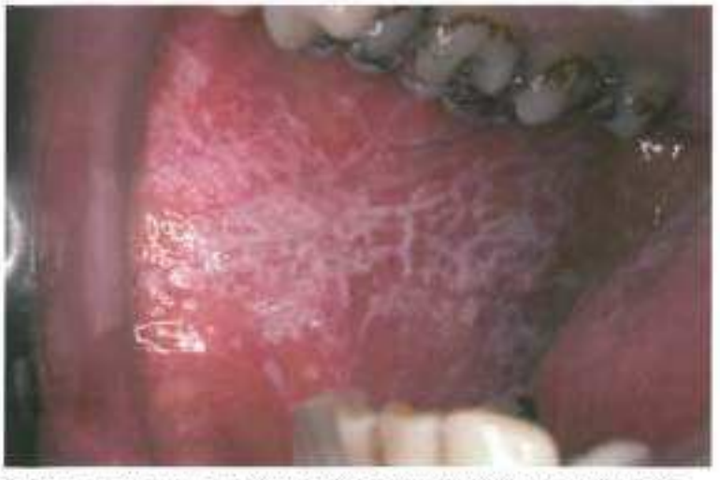


Fig. 7.55 Lichen planus. The white reticular pattern on the buccal mucosa is typical.

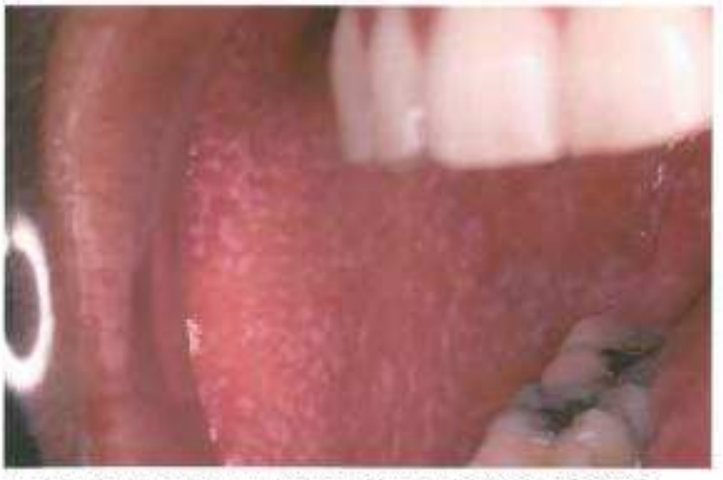


Fig. 7.56 Oral lichen planus. White papules usually arranged in a net-like configuration are the most common finding.

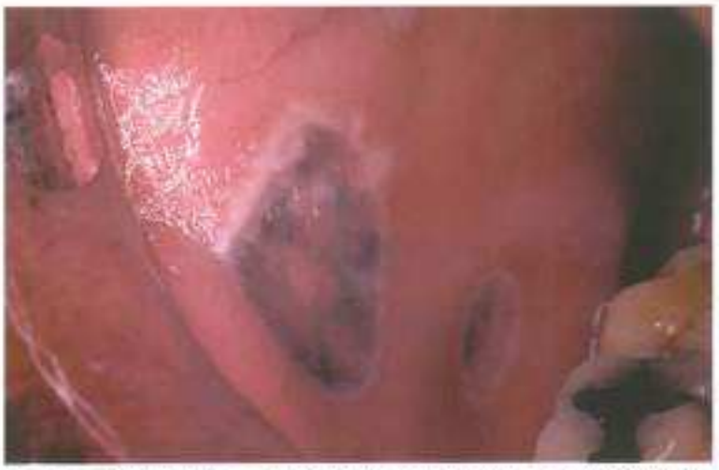


Fig. 7.57 Oral lichen planus. In black skin, postinflammatory pigmentation may be prominent. The surrounding white rim is prominent. This is the same patient as in Fig. 7.12.

- **Oral lichen planus** Oral lesions are common and are usually present on the buccal mucosae as a white reticulate pattern (Figs 7.55 and 7.56). They may be annular and hyperpigmented in a black skin (Fig 7.57). They are usually asymptomatic and serve to confirm the diagnosis of the accompanying skin rash. Sometimes, however, changes occur alone either as white plaques on the tongue (Figs 7.58 and 7.59) and lips (Figs 7.60 and 7.61) or as erosive or ulcerative lesions

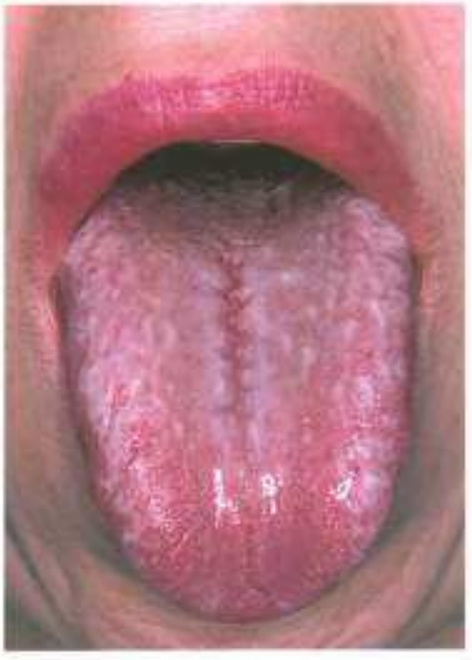


Fig. 7.58 Oral lichen planus. The tongue is strikingly involved, with white plaques. This may occur in isolation or associated with skin lesions (Fig. 7.10), which aids the diagnosis. A biopsy may otherwise be necessary.

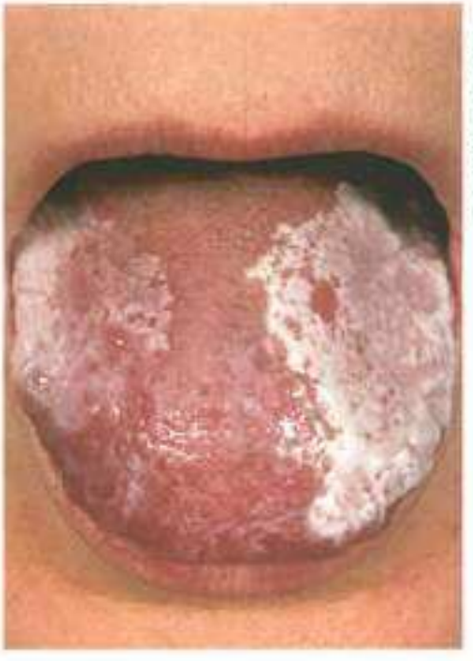


Fig. 7.59 Oral lichen planus. White patches in the mouth (and vulva) have erroneously been called leukoplakia and associated with malignancy. A biopsy confirmed this as lichen planus.

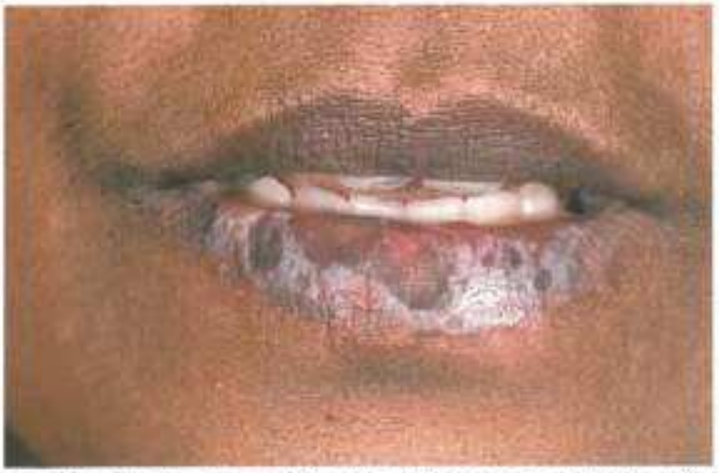


Fig. 7.60 Oral lichen planus. White net-like lesions, some of which have resulted in pigmentation, are present on the lower lip. (By courtesy of Dr A. C. Pembroke.)

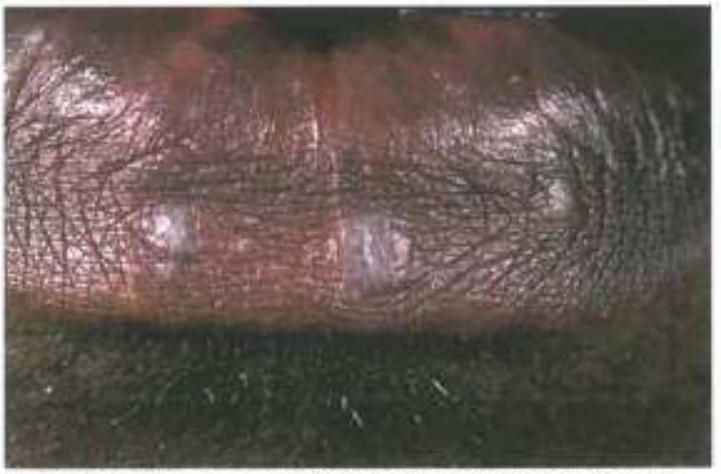


Fig. 7.61 Oral lichen planus. There are tiny and slightly larger papules on the lips. They are highly characteristic of lichen planus and respond to superpotent steroids.

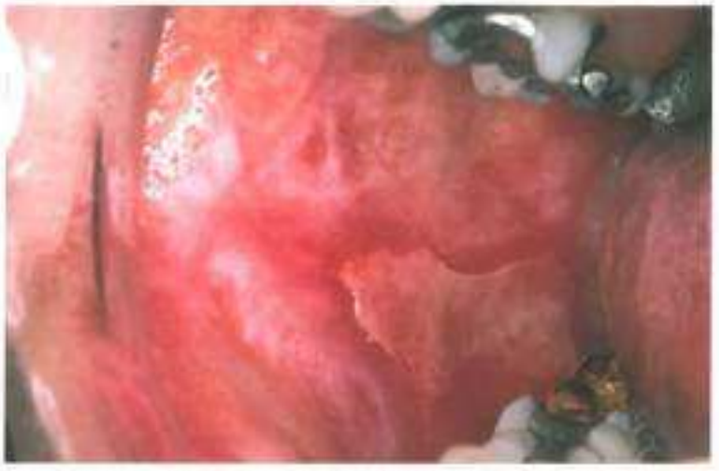


Fig. 7.62 Erosive lichen planus. Eroded areas are visible amongst the background of white streaks. Similar lesions may occur on the skin and are not easy to treat.

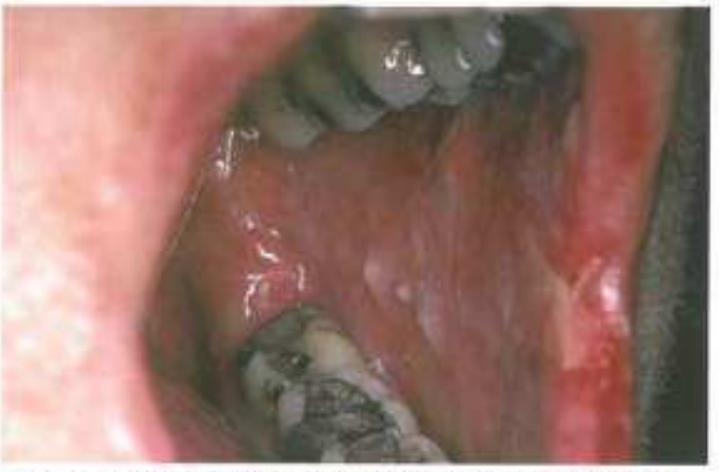


Fig. 7.63 Amalgam lichenoid reaction. White patches are present but in this case are secondary to the dental amalgams. The patient was positive to mercury on patch testing and the lesions cleared after replacing them.

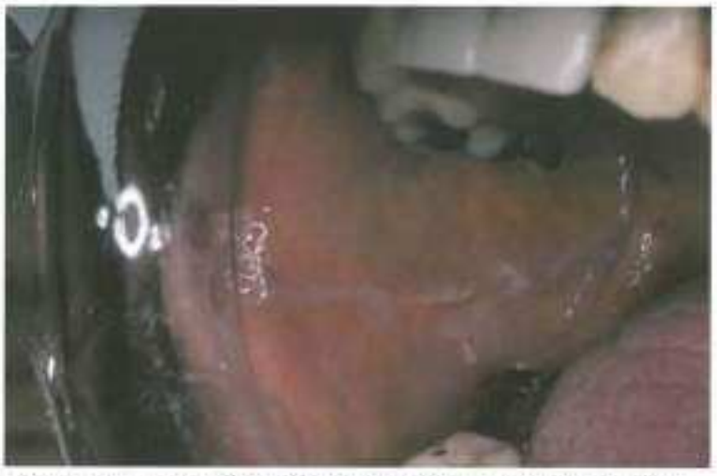


Fig. 7.64 Trauma. A horizontal white linear thickening is present from repeated biting of the buccal mucosa.

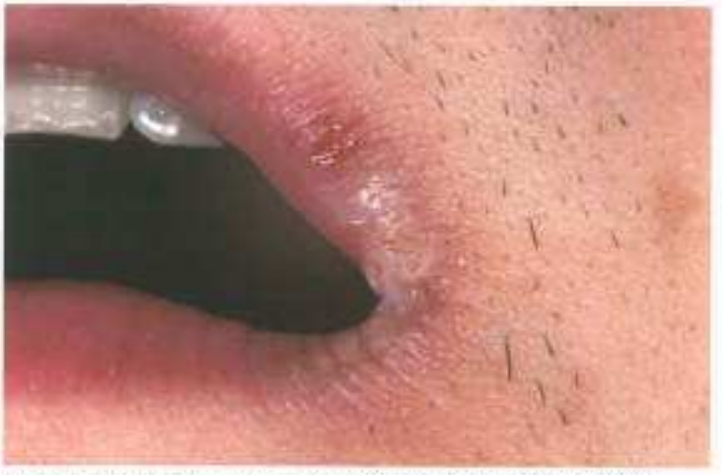


Fig. 7.65 Traumatic leucokeratosis. Thickened, white patches may result inside or outside the mouth from traumatizing the area with the teeth. Biopsy will establish the benign nature of the white warty patch.

(Fig. 7.62) on the gums, buccal mucosae and tongue. White streaks may be seen round the ulcers, which help to make the diagnosis, but a biopsy is necessary and follow-up is advisable because very occasionally a squamous cell carcinoma may develop. Non-steroidal anti-inflammatory drugs may cause oral erosive lichen planus. Dental amalgams (Fig. 7.63) may produce lichenoid reactions which resolve on replacing the amalgams. The white lace-like patterning is asymmetrical and adjacent to the amalgam; consequently, the diagnosis is not difficult but it should be confirmed with patch testing.

Other conditions to be considered in the differential diagnosis of buccal mucosal and lip lesions are trauma (Figs 7.64 and 7.65) and of tongue disorders, are geographical (Figs 7.66 and 7.67) and black hairy tongue (Fig. 7.68) and also racial pigmentation (Fig. 7.69).

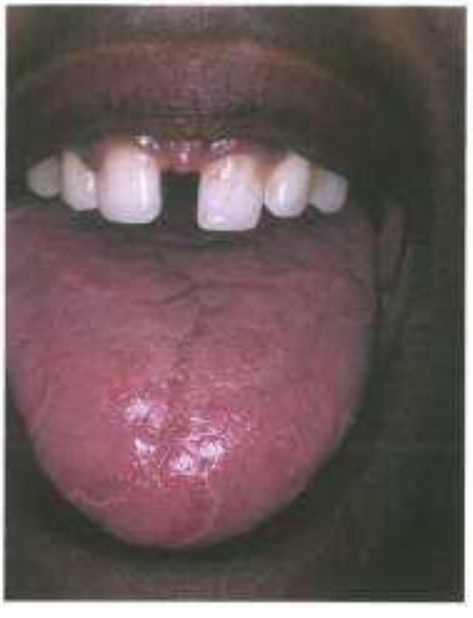


Fig. 7.66 Geographical tongue. This is a common developmental abnormality of no significance. Deep fissures may occur and it is sometimes known as a scrotal tongue.

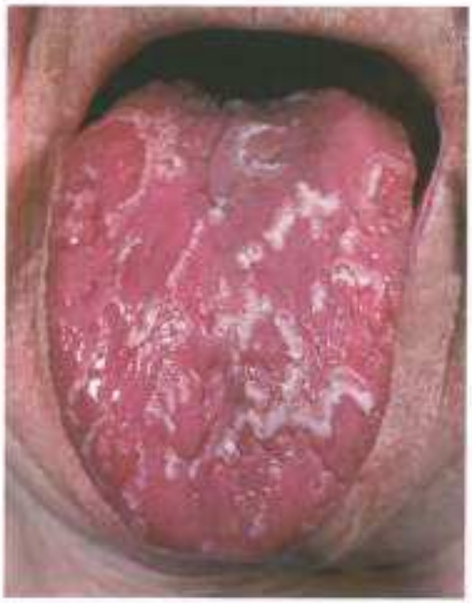


Fig. 7.67 Geographical tongue. The white, eroded areas change their configuration and position constantly. It is another appearance of the scrotal tongue.

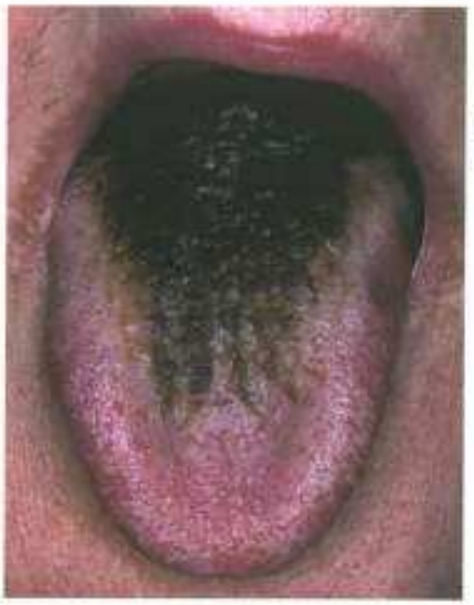


Fig. 7.68 Black hairy tongue. The appearance is instantly recognizable; it may be caused by overgrowth of *Candida* species following broad-spectrum antibiotics.

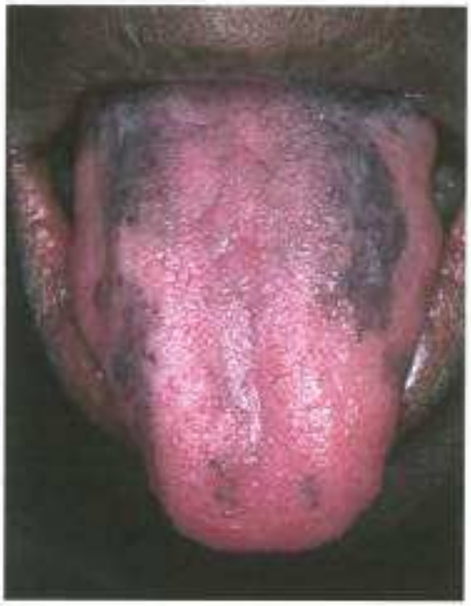


Fig. 7.69 Racial pigmentation. Pigmented macules are common and perfectly normal in blacks.

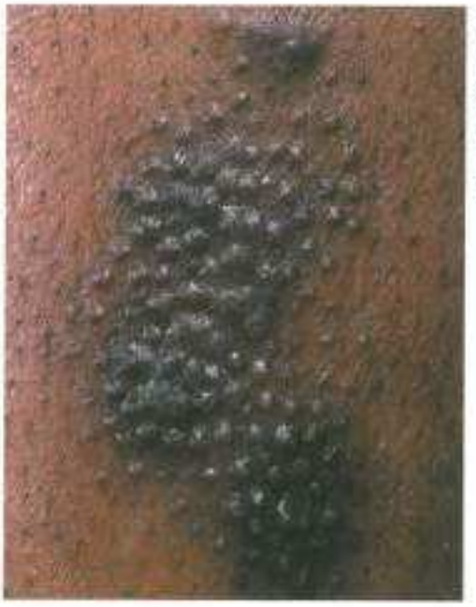


Fig. 7.70 Lichenoid eczema. The lesions may simulate lichen planus because the papules are itchy and may be quite flat topped but they are not shiny or purple.

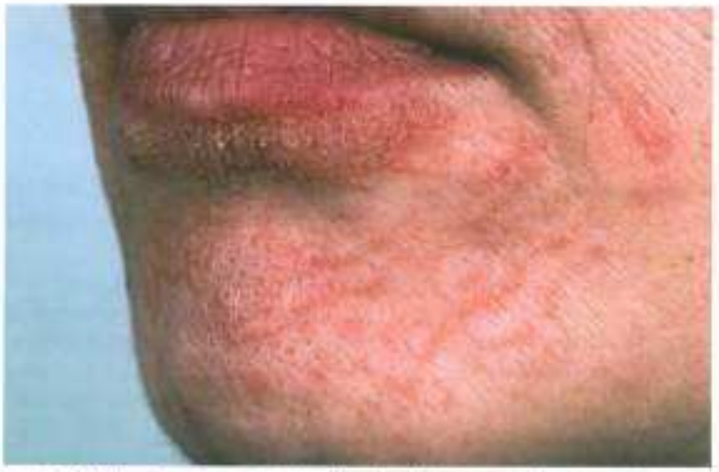


Fig. 7.71 Nekam's disease. In this disorder of unknown aetiology but which may be a variant of lichen planus, the papules are monomorphic and often arranged in a linear pattern.

Differential Diagnosis

The diagnosis is mostly based on clinical observation. Isolated annular lesions may easily be misdiagnosed, but biopsy is unequivocal if there is doubt because the histology is so specific. The diseases that cause confusion are other papular disorders.

- **Lichenoid eczema** (Fig. 7.70).
- **Nekam's disease** (Keratosis lichenoides chronica) This is regarded by some, but not all, as a variant of lichen planus. There are purplish monomorphic lesions arranged in a linear (Fig. 7.71), reticular or papular pattern on the face, limbs and trunk. There may be an

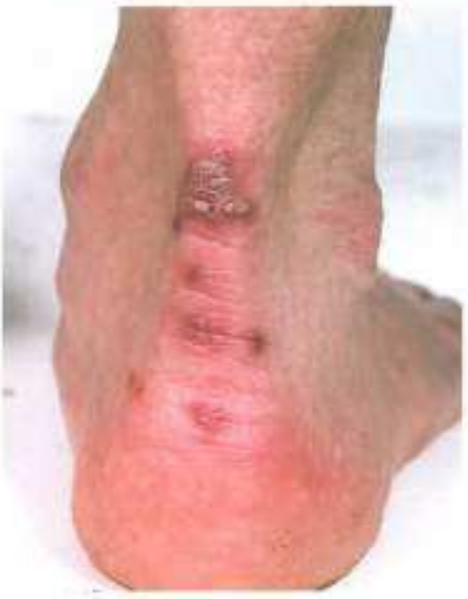


Fig. 7.72 Nekam's disease. The lesions may be quite keratotic and purple in colour. The pathology is of a lichenoid dermatitis. It is very rare.

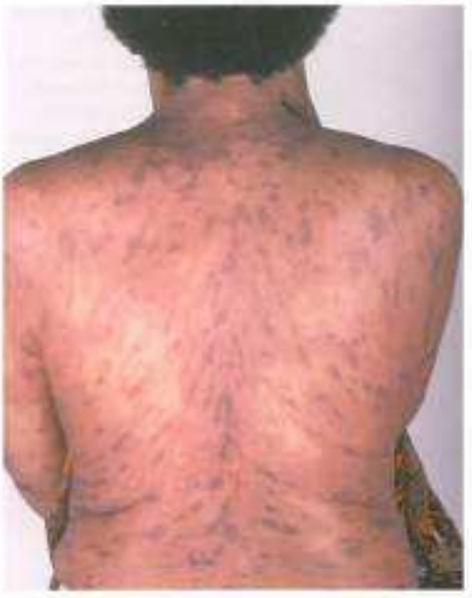


Fig. 7.73 Lichenoid drug eruption. The purple colour is still discernible. This was caused by gold. A biopsy may be helpful because eosinophils are often present, which they are not in classical lichen planus.

infundibulum or acrosyringium in the centre of the papule. They may be keratotic on the feet (Fig. 7.72). It is a lichenoid dermatitis with numerous necrotic keratinocytes and parakeratosis.

- **Scabies** (Ch. 16) Scabies and lichen planus are very itchy but in lichen planus there are no burrows, the lesions are rarely excoriated and the purple colour is striking.
- **Guttate psoriasis** (Fig. 7.17).
- **Lichenoid drug eruptions** Gold, streptomycin, isoniazid, ethambutol, carbamazepine, chlorpromazine, captopril, enalapril, penicillamine, thiazides, demeclocycline, quinine and mepacrine have all been recorded as causing lichenoid eruptions. Sometimes there is a photosensitive component to the eruption, particularly with thiazides, demeclocycline and quinine. The reactions can be quite severe and resolution slow despite withdrawal of the drug. Postinflammatory pigmentation may be considerable in dark skins (Fig. 7.73).
- **Lichenoid actinic keratosis** This is a solitary purple lesion occurring in a site of photodamage. The histology is similar to lichen planus (Fig. 7.74).
- **Graft-versus-host disease** (Ch. 18).

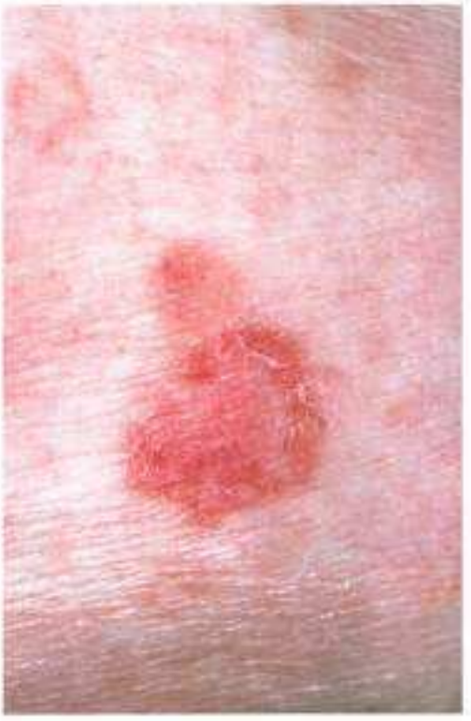


Fig. 7.74 Lichenoid actinic keratosis. The lesion is solitary and is a form of actinic keratosis but the histology of this lesion was that of lichen planus. However, the clinical context distinguishes the two.

Management

Some 50% of patients are clear within 9 months and 85% within 18 months. The remainder usually have variants, such as complicated oral lesions or hypertrophic plaques. Ordinary lichen planus very rarely recurs. Lichen planus may be treated in several ways:

- **Topical steroids** Therapy has been revolutionized by superpotent steroids. The itch is quickly alleviated and active purple papules are flattened and become pigmented. The steroid will not help the post-inflammatory hyperpigmentation, however.
- **Systemic steroids** These are sometimes necessary for particularly widespread and troublesome disease, or when it involves important functional areas, such as the hands and feet. Prednisolone is used, with 30–35 mg a reasonable starting dose. A reduction of 5 mg per week is made until a 15 mg dose is reached, and then reductions are by 2.5 mg weekly. Occasionally second courses are required.
- **Ciclosporin** Systemic ciclosporin A may be effective.
- **Antihistamines** Sedative antihistamines are occasionally indicated for the itch.
- **Hypertrophic lichen planus** Hypertrophic lichen planus is difficult to manage but superpotent topical steroids enhanced by polythene occlusion, or intralesional triamcinolone may be helpful.
- **Oral lesions** Special formulations, such as triamcinolone acetonide in orabase, facilitate the adherence of the steroid to the oral mucosae. If this fails then a superpotent steroid ointment can be applied directly to the lesions. Occasionally, systemic steroids are required for ulcerative lichen planus, but their long-term effects are disappointing and side-effects are common. Similarly, acitretin, griseofulvin, ciclosporin A and mycophenolate mofetil may be tried. A 308 nm excimer laser treatment using a flexible fibreoptic delivery system has been reported as being effective.

Naevi and developmental defects

8

Naevi are benign proliferations of cells that are normally present in the skin. Thus a melanocytic naevus (commonly referred to as a mole) is a benign proliferation of melanocytes, which are found in the basal layer of the epidermis (Ch. 11.) and an epidermal naevus is a proliferation of keratinocytes arising from embryonic ectoderm. Since ectodermal cells are pluripotential and may form not only keratinocytes but also skin appendages, there may be a proliferation of more than one cell so that an epidermal naevus is technically a hamartoma because more than one normal component of the skin is present.

Some naevi have malignant potential, for example, sebaceous naevi. Some may form part of a syndrome; for example, connective tissue naevi are associated with tuberous sclerosus; some are present at birth and others, such as Becker's naevus, develop later.

Naevi are common and all individuals have such blemishes, especially melanocytic naevi, and sometimes in profusion. Patients may consult doctors about them for cosmetic reasons or because they are anxious as to their nature. Many can be diagnosed by simple inspection, and the physician can often predict whether the lesion is benign or potentially malignant. It may also be possible to assess whether the naevus will resolve spontaneously and is therefore best left alone, whether it can be removed simply, or requires a dermatological surgeon.

Epidermal naevi

EPIDERMAL NAEVUS

A lesion arising from embryonic ectoderma, composed almost exclusively of keratinocytes.

Aetiology

Epidermal naevi occur in both sexes and are usually present at birth. They may be associated with certain syndromes, for example Proteus (a characteristic but not invariable finding), CHILD (a constant association, although the clinical features, distribution and histology are different), McCune–Albright and Klippel–Trenaunay syndromes. Their appearance as linear streaks or swirls along the lines of Blaschko led Happle to propose that they are examples of genetic mosaicism caused by somatic postzygotic mutations, where two or more heterogeneous populations of cells arise within the same zygote. The lines of Blaschko are thought to represent the pattern of embryological migration of skin cells, giving rise to linear eruptions on the extremities, S-shaped curves on the abdomen and V-shaped ones rather like a fountain on the spine. They are explained by a combination of the transverse clonal proliferation from the primitive streak with the longitudinal growth and flexion of the embryo during development. This has become of interest because many verrucous epidermal naevi have the histology of epidermolytic hyperkeratosis and are due to mutation mosaicism in the gene for keratin 10 and thus if every cell in the body of an offspring were affected, bullous ichthyosiform erythroderma could result. Therefore, genetic counselling becomes important. Equally, epidermal naevi with an acantholytic or Darier-like histology, a late appearing epidermal naevus, may result from a mosaicism for the Darier gene and, therefore, there is a risk of development of Darier's disease in future generations. The rare linear porokeratotic epidermal naevus also occurs along the lines of Blaschko and may represent mosaicism for the gene responsible for porokeratosis of Mibelli, for which it has similar histological and clinical features.

Clinical Features

Symptoms

Usually present at birth or within the first decade; it may increase in size at puberty. Certain clinical subtypes are distinguished by their arrangement.

- **Naevus verrucosus** This begins as a pink or slightly pigmented velvety plaque or streak that gradually becomes darker and more verrucous, with a rough fissured surface (Fig. 8.1). They may be unilateral (Fig. 8.2) (*naevus unius lateralis*), multiple or linear (Fig. 8.3).

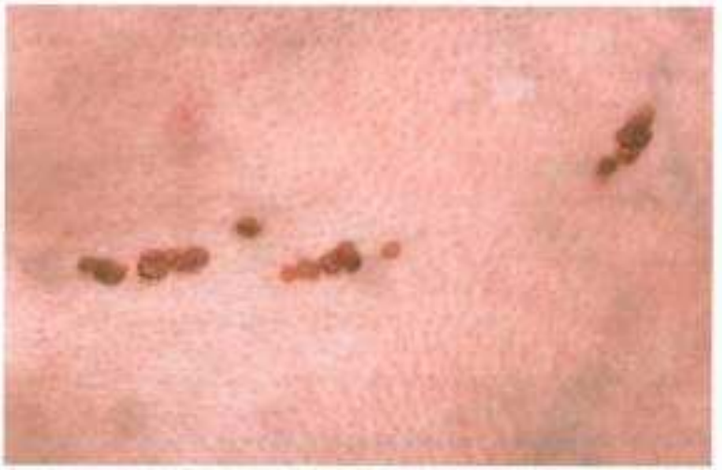


Fig. 8.1 Epidermal naevus. The lesion is well defined and has a rough warty surface. It resembles a seborrhoeic wart but is present at birth, and recurs after curettage. If required it should be excised.

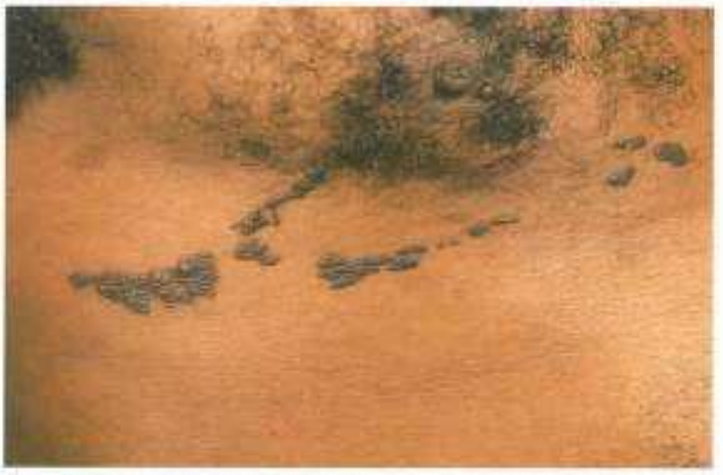


Fig. 8.2 Naevus unius lateralis. The naevus may be distributed in a linear and unilateral pattern.

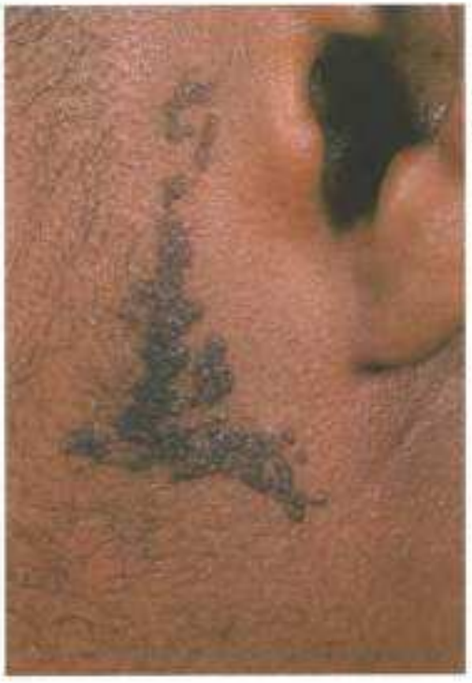


Fig. 8.3 Epidermal naevus. They are frequently linear in configuration, following the lines of embryological migration of skin cells (lines of Blaschko). (Courtesy of Dr Elisabeth Higgins.)

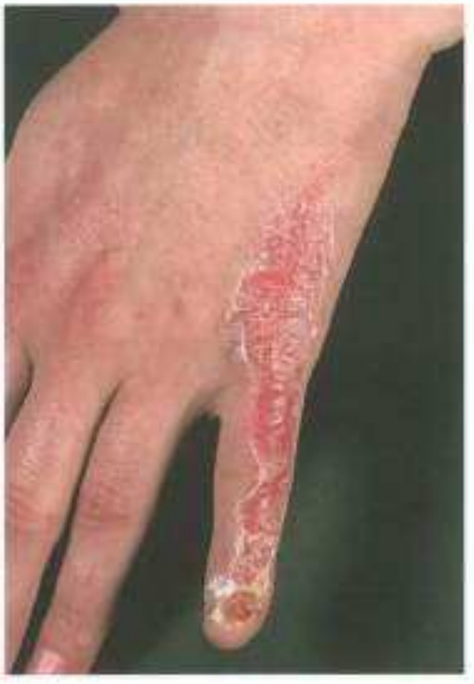


Fig. 8.4 Inflammatory linear verrucous epidermal naevus (ILVEN). Occasionally an inflammatory component is present. The lesions are very pruritic and may involve a limb or finger (including the nail).

- **Inflammatory linear verrucous epidermal naevus (ILVEN)** Occasionally a linear epidermal naevus may have an inflammatory component. It is pruritic, occurs along a limb and may involve the nail (Fig. 8.4).
- **Ichthyosis hystrix** This is bilateral and extensive (Fig. 8.5) over a zosteriform and systematized area (*Ichthyosis hystrix*).

Histopathology

Most epidermal naevi are a simple squamous papilloma showing hyperkeratosis, papillomatosis and acanthosis (Fig. 8.6). Some have seborrhoeic wart-like features. Occasionally, there is massive hyperkeratosis overlying an acanthotic epidermis with marked vacuolation and abundant irregular keratohyaline-like material (epidermolytic hyperkeratosis). Some may have acantholytic features simulating Darier's or Hailey Hailey disease. ILVEN has a rather dermatitic histology with some features of psoriasis. A porokeratotic type has a cornoid lamella (a column of parakeratosis located above a dell in the surface of the epithelium).

Differential Diagnosis

- **Viral warts** These may occur in a linear pattern, particularly plane warts, but are not present at birth.
- **Lichen striatus** This is a self-limiting linear form of eczema that usually starts in childhood. The papules are lichenoid and are arranged in a linear or zosteriform pattern, often becoming hypopigmented.
- **Incontinentia pigmenti** This condition is present at birth and does have a linear pattern but the initial lesions are vesicular, but subsequently verrucous and pigmented.
- **Seborrhoeic wart** Often indistinguishable but not present at birth.

Management

Whereas a seborrhoeic wart can be removed simply by curettage and cautery or cryotherapy, an epidermal naevus must be excised, because the epidermal proliferation and differentiation is determined by the dermis and the naevus will recur after ablative therapy. There have been reports of the effective use of lasers. Some authorities believe that all epidermal naevi should be biopsied because of the genetic risk of the epidermolytic variety. Very occasionally, basal and squamous cell carcinomas may develop.

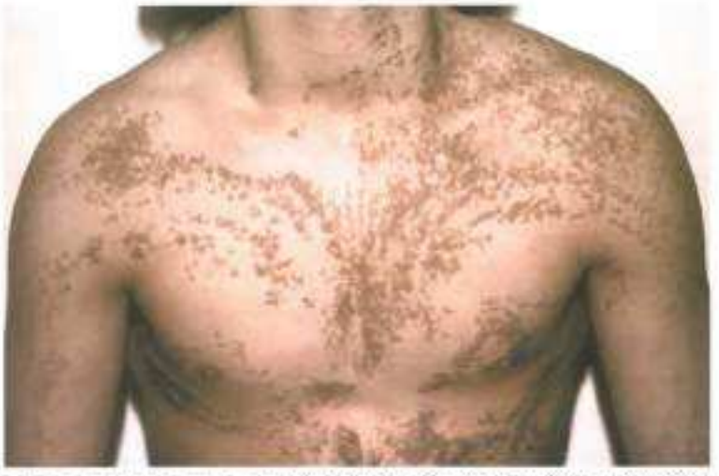


Fig. 8.5 Ichthyosis hystrix. The epidermal naevi occur bilaterally and extensively in a zosteriform manner. This fountain-like shape along the lines of Blaschko is produced by the longitudinal growth and flexion of embryonic growth.

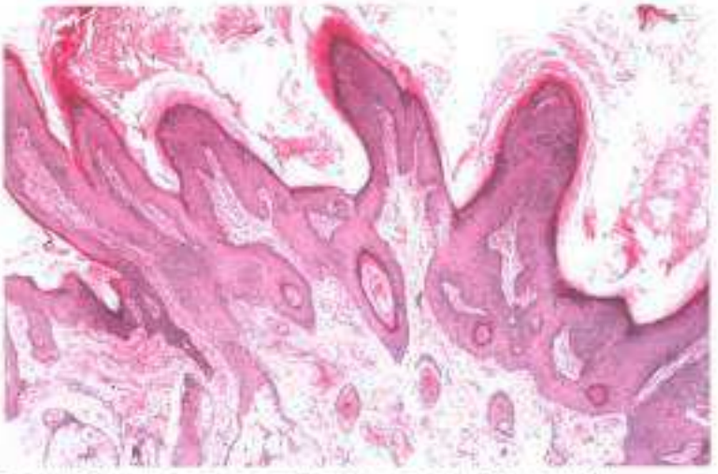


Fig. 8.6 Epidermal naevus, papillomatous variant. There is marked papillomatosis with a prominent granular cell layer and hyper (ortho) keratosis. The epidermal ridges are accentuated and partly fused.

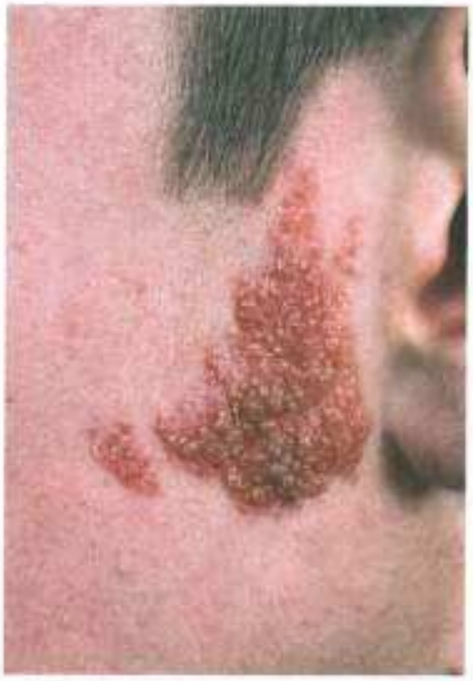


Fig. 8.7 Sebaceous naevus. The lesion is a yellowish plaque. It has a predilection for the scalp and face. It becomes prominent after puberty and subsequently may progress to a basal cell carcinoma.

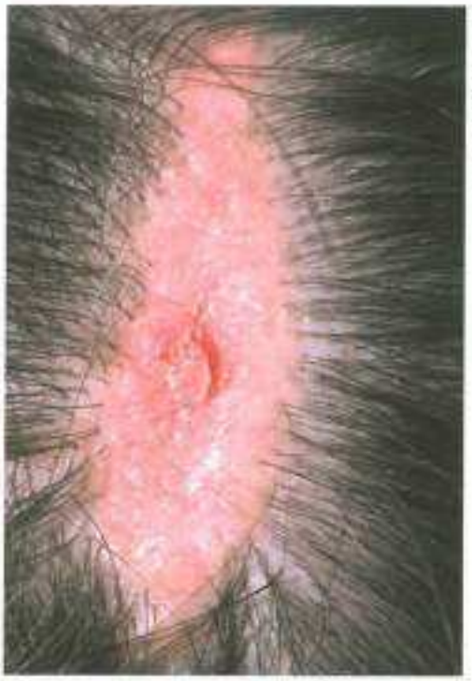


Fig. 8.8 Sebaceous naevus. The sebaceous glands are androgen-sensitive so the naevus may increase in size during infancy but subsequently regress until puberty.

SEBACEOUS NAEVUS

A yellow plaque usually present at birth on the head or neck.

Clinical Features

Symptoms

Although present at birth, the lesion may be quite flat and inconspicuous and not noticed until puberty when it grows to reach its maximum size. It is an androgen-sensitive tumour and may increase in size in infancy, like the sebaceous glands, but subsequently regress until puberty.

Morphology

The lesion is a raised, hairless, yellow or orange plaque that is surmounted by many rounded elevations (Fig. 8.7).

Distribution

The head (especially the scalp; Figs 8.8 and 8.9), face (Fig. 8.10) and neck.

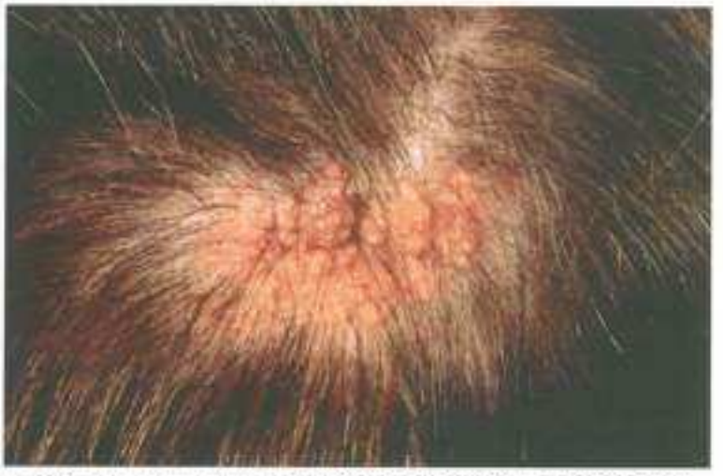


Fig. 8.9 Sebaceous naevus. This androgen-sensitive naevus is inconspicuous after infancy but in adolescence becomes a well-defined yellow mamillated plaque. The scalp and face are common sites.

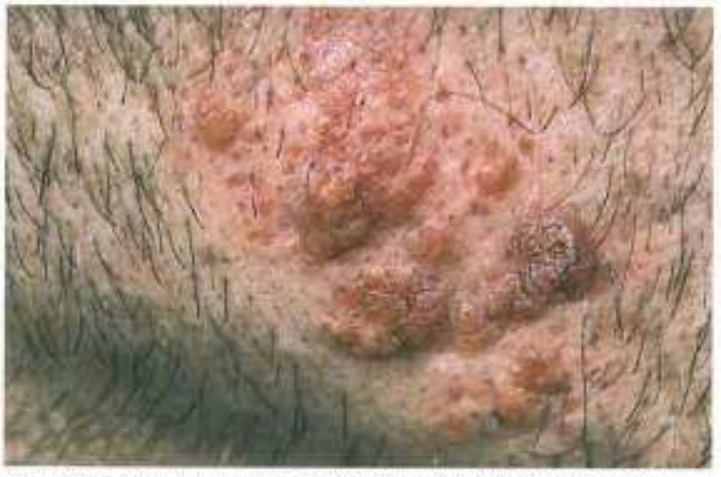


Fig. 8.10 Sebaceous naevus. The plaque is surmounted by many rounded ('mamillated') elevations and is entirely hairless. The orange hue is pronounced here.

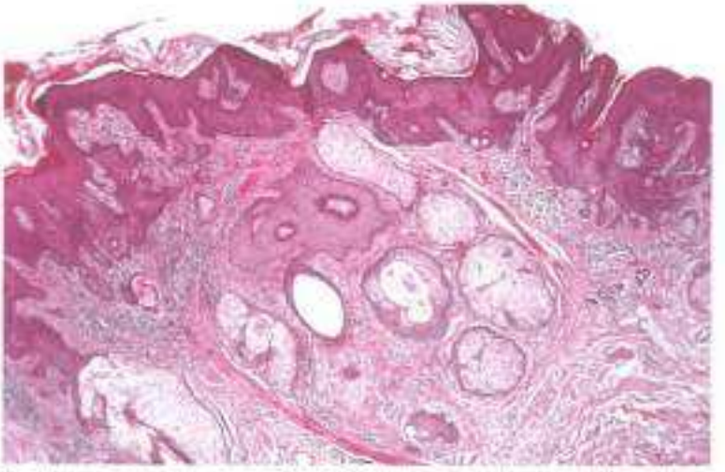


Fig. 8.11 Sebaceous naevus. The epidermis is irregular, hyperkeratotic and has a rather verrucous surface. Abundant abnormal sebaceous glands are present.

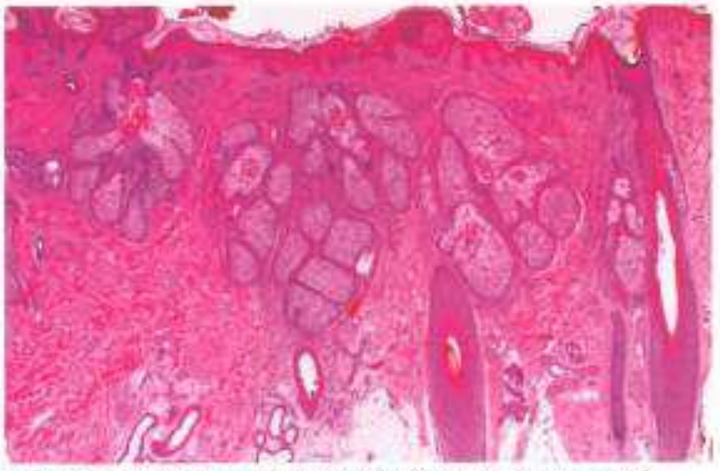


Fig. 8.12 Sebaceous naevus. The epidermis is papillomatous. There are numerous sebaceous glands high in the dermis and ectopic apocrine glands in the deep dermis. (Courtesy of Dr Jon Salisbury)

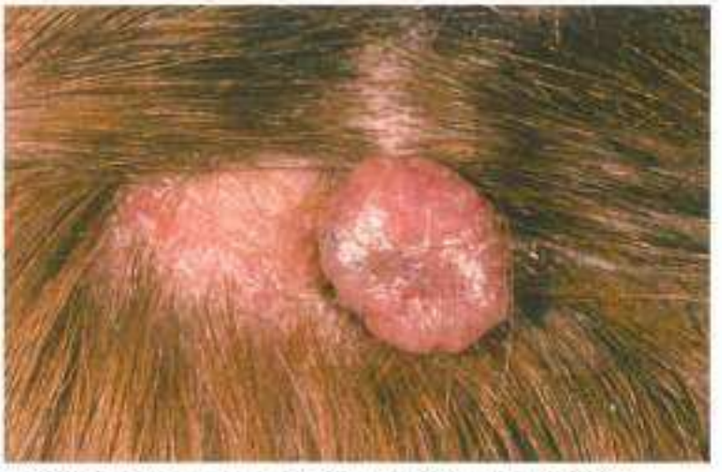


Fig. 8.13 Sebaceous naevus and basal cell carcinoma. Unlike other epidermal naevi, sebaceous naevi often develop into basal cell carcinoma (the nodule on the right side of the plaque) and prophylactic excision is wise.

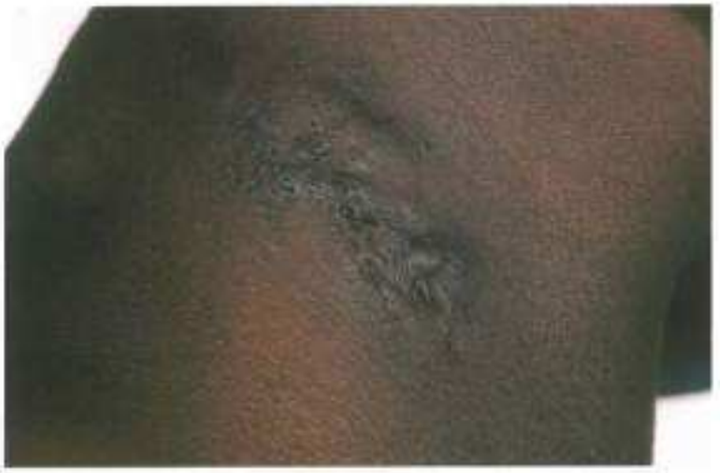


Fig. 8.14 Naevus acneiformis. A comedo naevus may be complicated by chronic inflammation and suppuration and simulate acne and is known as naevus acneiformis.

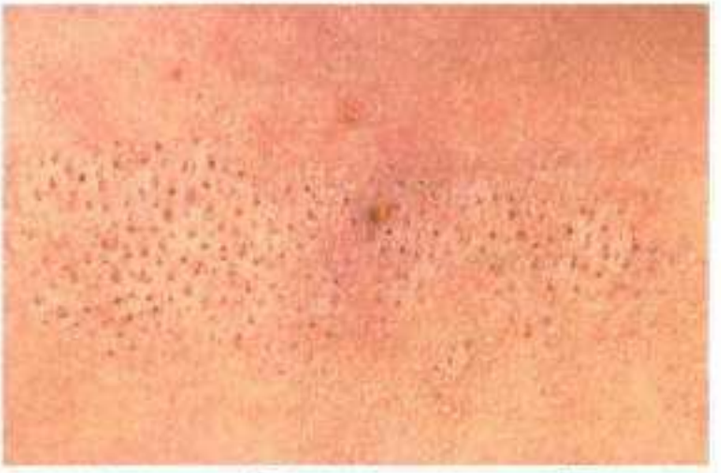


Fig. 8.15 Comedo naevus. The lesion is linear and composed of blackheads. Inflammatory acneiform lesions may occur.

Histopathology

The features are variable, but once established the squamous epithelium is acanthotic and frequently papillomatous. Sebaceous glands are abundant (Fig.8.11), hypertrophied, distorted, and situated abnormally high in the dermis (Fig. 8.12), sometimes communicating directly with the surface epithelium. Common findings are small, immature hair follicles (hair germs) situated close to or apparently arising from the surface epithelium or sebaceous glands and ectopic apocrine glands situated deep in the dermis or subcutaneous fat. Mature hair follicles are reduced in number or absent.

Management

Since sebaceous naevi arise from pluripotential epithelial stem cells, they may dedifferentiate in later life into secondary benign, e.g. syringocystadenoma papilliferum or malignant tumours, e.g. basal cell carcinoma (Fig. 8.13) and occasionally squamous cell, sebaceous or apocrine carcinomas. Prophylactic excision is, therefore, advisable. Photodynamic therapy may produce excellent results.

A rare disorder is the *Schimmelpenning–Feuerstein–Mims* or *Solomon syndrome*. It is a subset of the epidermal naevus syndrome. This is a *linear sebaceous naevus* associated with neurological (including epilepsy and mental deficiency), ophthalmological, skeletal, cardiovascular and urological defects. There is genomic mosaicism in stem cells, which expand in the distribution of Blaschko's lines. It is largely sporadic.

Follicular naevi

COMEDO NAEVUS

A developmental, often linear, abnormality of the hair follicle that results in numerous keratin-filled pits which resemble blackheads.

Clinical Features

Symptoms

Usually asymptomatic, it normally presents in childhood or adolescence.

Morphology

Blackheads mainly but may be complicated by chronic inflammation, suppuration, fistula formation and scarring (*naevus acneiformis* [Fig. 8.14]).

Distribution

Often linear (Fig. 8.15) particularly on the face or occasionally multiple lesions on the neck, trunk or arms.

Histopathology

Large numbers of cystically dilated hair follicles arise from an atrophic epidermis (Fig. 8.16).

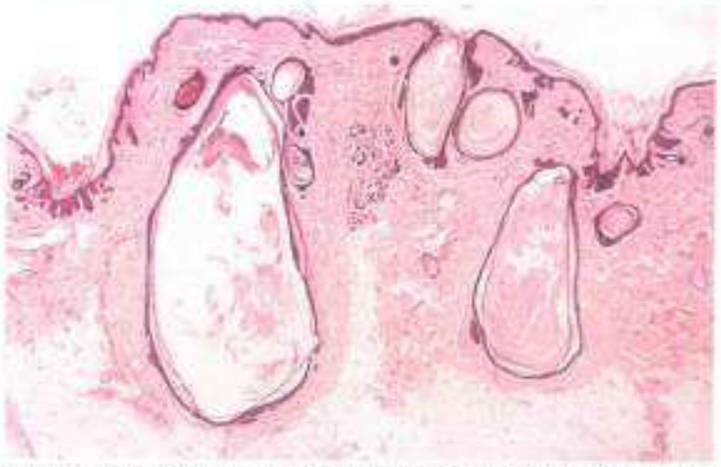


Fig. 8.16 Comedo naevus. Large numbers of cystically dilated hair follicles arise from an atrophic epidermis. Both open and closed comedones are present.

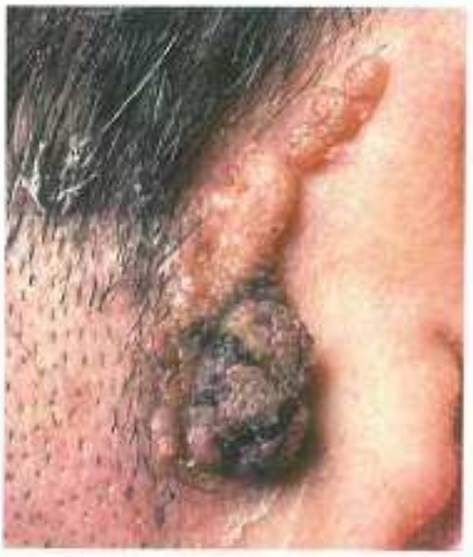


Fig. 8.17 Syringocystadenoma papilliferum. This is often linear, tends to be associated with naevus sebaceous and is usually on the head and face; basal cell carcinomatous change has occurred at the lowest part of this lesion behind the ear. (Courtesy of the late Dr Neil Smith.)

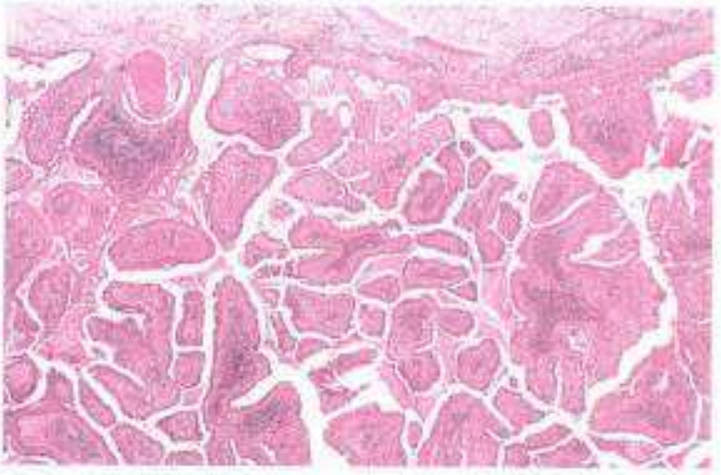


Fig. 8.18 Syringocystadenoma papilliferum. The lesion is characterized by a warty, exophytic configuration. Numerous villous papillary projections extend into the lumina with cystic invaginations.

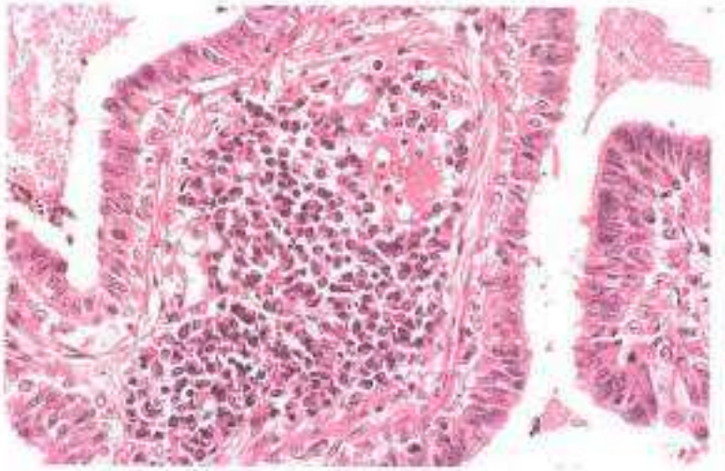


Fig. 8.19 Syringocystadenoma papilliferum. There is a double layer of epithelial cells. The inner is composed of tall columnar and outer of small cuboidal cells. There is an intense plasma cell infiltrate.

Management

Surgery is the treatment of choice. Topical retinoic acid has some effect, but oral isotretinoin is ineffective, except possibly in patients with multiple lesions.

Apocrine naevi

SYRINGOCYSTADENOMA PAPILLIFERUM

A developmental abnormality of the apocrine and eccrine sweat glands.

Clinical Features

Symptoms

An asymptomatic mark, present at birth or early childhood, usually on the head and neck.

Morphology and distribution

There are three types.

- **The solitary form** This appears as single or multiple warty plaques, particularly on the shoulders, axillae or genito-crural areas at puberty.
- **The plaque form** Similar to a naevus sebaceous, with which it may be associated, it occurs on the scalp and is present at birth or develops in childhood. The plaque comprises numerous yellow or brown papules, often with a central ostium. It is devoid of hair. At puberty it becomes more elevated, nodular and verrucous.
- **The linear variety** This occurs on the neck or face and consists of a group of nodules (Fig. 8.17).

Histopathology

The lesion may occur as an invagination or an outgrowth of the epidermis. There are papillae lined with two layers of epithelium that communicate with ducts (Fig. 8.18), which have an inner layer of columnar cells, with an eosinophilic cytoplasm, and an outer one of cuboidal cells, with hyperchromatic nuclei. There are numerous plasma cells in the stroma (Fig. 8.19).

Management

There is a 10% risk of transformation into a basal or, very occasionally, squamous cell carcinoma, usually in association with naevus sebaceous. Excision is the preferred treatment. These naevi are associated with the epidermal naevus syndrome.

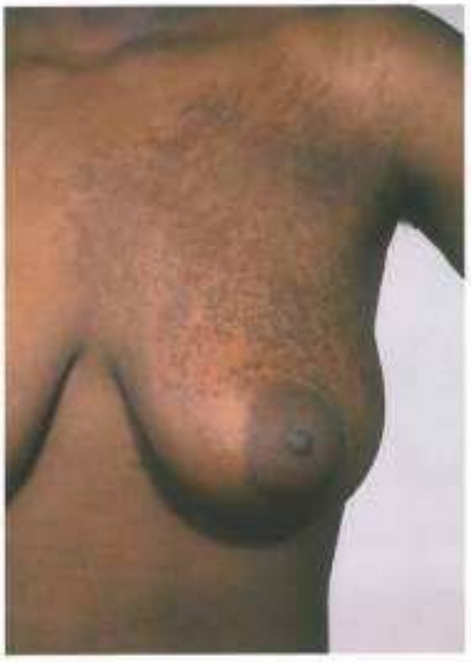


Fig. 8.20 Becker's naevus. Initially the lesion is an irregular macular pigmentation. Androgen receptors are increased and it usually commences in adolescence. The front of the chest is a common site.

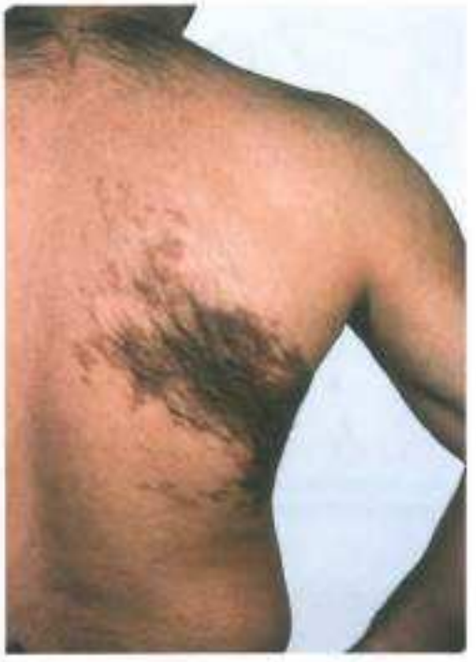


Fig. 8.21 Becker's naevus. It is unilateral. The back of the shoulder is a characteristic site. The hypertrichosis becomes evident at puberty.

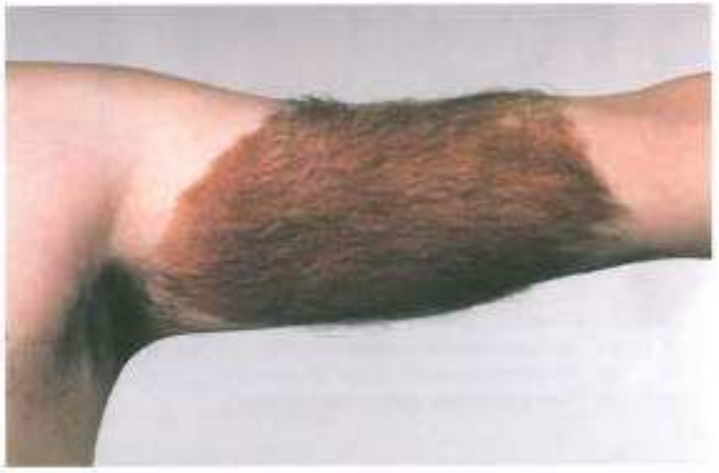


Fig. 8.22 Becker's naevus. This is an androgen-sensitive epidermal naevus that becomes apparent at puberty as a flat area of pigmentation, and subsequently may become hairy.

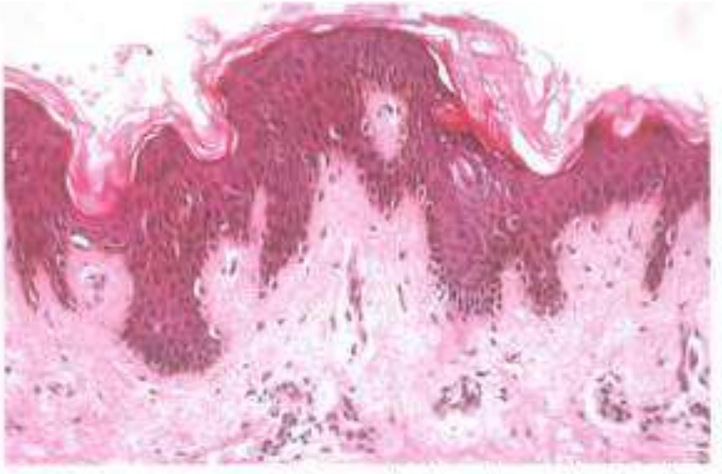


Fig. 8.23 Becker's naevus. A high-power view shows increased numbers of melanocytes and conspicuous epidermal pigmentation.

BECKER'S NAEVUS

An androgen-mediated hyperplasia resulting in an extensive pigmented, often hairy, epidermal naevus, occurring at puberty, particularly in males.

Clinical Features

Symptoms

It appears during adolescence.

Morphology

Becker's naevus is flat and pigmented initially (Fig. 8.20) but subsequently may become raised and develop thick coarse hairs (Fig. 8.21).

Distribution

The back of the shoulder (Fig. 8.22), the front of the upper chest and the upper arms, but it may occur anywhere.

Histopathology

The features may be quite difficult to discern, but in an established lesion the changes are those of mild hyperkeratosis, focal acanthosis, with a slight increase in the granular cell layer, and perhaps an accentuation of the epidermal ridge pattern. There is marked pigmentation of the basal layer associated with increased numbers of melanocytes (Fig. 8.23) and pigmentary incontinence. The hair follicles appear normal and there is no evidence of melanocytic naevus formation. There may be abundant smooth muscle bundles in the dermis and hypertrophy of the arrector pili muscles.

Management

The diagnosis is not difficult. There is no effective treatment and simple reassurance is all that is required but there are reports of benefit from Q-switched ruby lasers.

There is a rare *pigmented hairy epidermal naevus syndrome*. This is the association of a Becker's naevus with spina bifida, unilateral hypoplasia of the breast in females and ipsilateral aplasia of the pectoralis muscle and limb shortening.

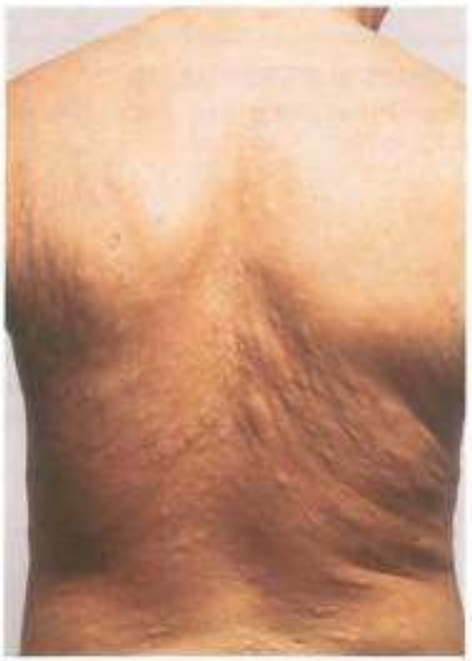


Fig. 8.24 Connective tissue naevi. Flesh-coloured raised plaques occur on the trunk. (By courtesy of St Mary's Hospital.)

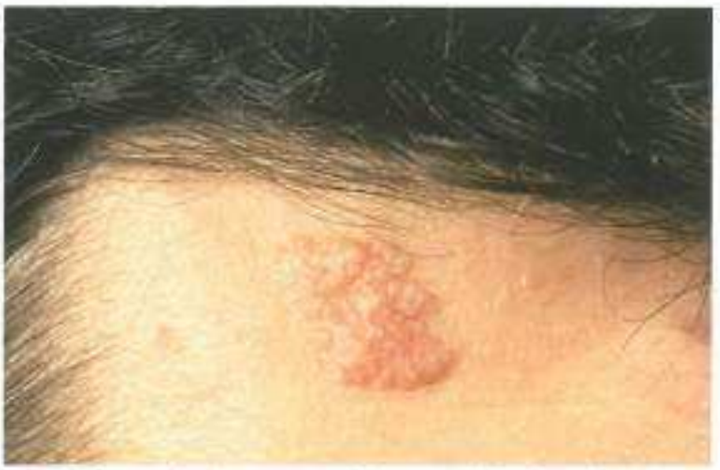


Fig. 8.25 Connective tissue naevus. A plaque consisting of many flesh-coloured papules (shagreen patch) can be seen on the forehead of a man with tuberous sclerosis.

EPIDERMAL NAEVUS SYNDROME

This syndrome is comprised of epidermal naevi (particularly verrucous, comedo, sebaceous naevi and syringocystadenoma papilliferum) with non-cutaneous developmental defects, particularly affecting the central nervous system, eye and skeleton. Half the patients do have neurological abnormalities, and these are associated with head and neck naevi, especially sebaceous naevi (Schimmelpenning–Feuerstein–Mims syndrome). Other syndromes are Solomon syndrome and *Jadassohn's naevus phakomatosis*. Seizures, mental deficiency and spastic hemiparesis are among the abnormalities and are associated with ipsilateral gyral malformations, hemimegalencephaly and other abnormalities. The eye may be involved by the naevus, but many abnormalities, including opacities and cataracts, are described. The skeletal abnormalities include kyphosis, scoliosis, cystic and lytic changes, hypertrophy and atrophy, short limbs and syndactyly. Malignant changes have been reported in the naevi. The condition should be distinguished from the Proteus syndrome and the CHILD syndrome.

Dermal and subcutaneous naevi

CONNECTIVE TISSUE NAEVUS

Circumscribed hamartomatous lesions of the dermal extracellular matrix, particularly collagen and elastic fibres, which may occur alone or as part of tuberous sclerosus (collagenomas) or the Buschke–Ollendorff syndrome (elastomas).

Aetiology

Collagenomas may:

- be inherited as an autosomal dominant condition (*familial cutaneous collagenoma*). Multiple indurated smooth, skin-coloured nodules are present on the thighs, buttocks and particularly the back (Fig. 8.24). The lesions usually appear in the second decade and there is an increased incidence of hypertension and cardiomyopathy.
- occur sporadically but may be clinically indistinguishable (*eruptive collagenomas*).
- occur as an isolated acquired collagenoma.
- occur in tuberous sclerosus and are known as shagreen patches (Fig. 8.25); they consist of irregular thickened plaques, usually seen on the lower back or forehead. They have a rather mamillated surface.

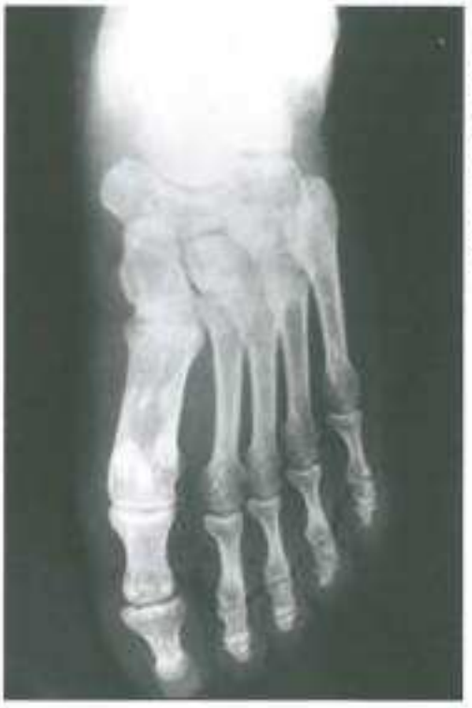


Fig. 8.26 Osteopoikilosis. Multiple small symmetric epimetaphyseal osteosclerotic foci occurring in association with connective tissue naevi is known as the Buschke-Ollendorf syndrome. (Courtesy of Dr P. Gishen.)

- occur as extensive plantar cerebriform collagenomas in the Proteus syndrome.

Elastomas may be associated with osteopoikilosis (Fig. 8.26) in the *Buschke–Ollendorff syndrome*. Osteopoikilosis (Greek 'spotted bones') refers to asymptomatic, irregular, radio-opaque lesions situated particularly within the long bones, pelvis, hands and feet. The elastomas may be symmetrical uniform small asymptomatic lichenoid papules (*dermatofibrosis lenticularis disseminata*) that are rather reminiscent of pseudoxanthoma elasticum or, more commonly, large yellow nodules that are grouped to form an asymmetrical plaque which is usually apparent before puberty. Otosclerosis may be present. It is inherited as an autosomal dominant but is often incompletely expressed. It is due to mutations in LEMD 3 gene, an inner nuclear membrane protein which antagonizes transforming growth factor β (TGF-β) and bone morphogenetic protein (BMP) signalling.

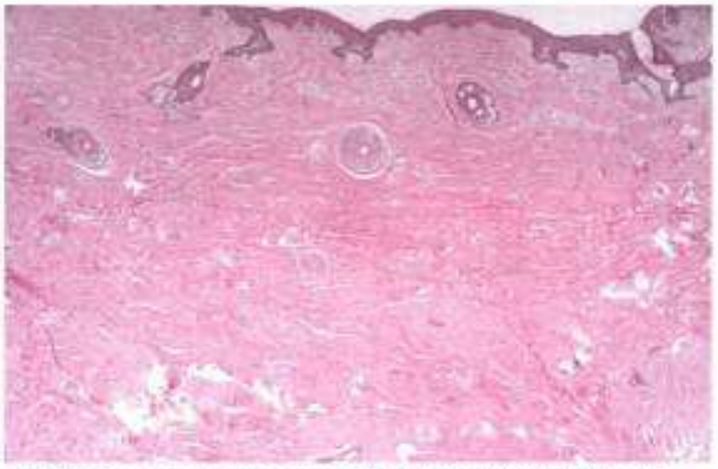


Fig. 8.27 Connective tissue naevus. The dermis is expanded by increased amounts of variably orientated broad bands of collagen.

Clinical Features

Symptoms

Connective tissue naevi are asymptomatic.

Morphology

Indurated smooth skin coloured mamillated plaques or nodules.

Distribution

Varied.

Histopathology

All collagenomas consist essentially of increased dermal collagen (Fig. 8.27). Elastic fibres may appear diminished, but whether this represents a real or apparent phenomenon is uncertain.

Juvenile elastoma often appears normal with haematoxylin and eosin but with elastic stains; thick interlacing tracks of elastic fibres are seen running between normal collagen in the reticular dermis.

Management

A solitary lesion may be excised.

Fat naevi

NAEVUS LIPOMATOSUS SUPERFICIALIS

A unilateral naevus characterized by multiple papules or plaques caused by ectopic mature lipocytes in the dermis.

Clinical Features

Symptoms

It may be present at birth or arise within the first two decades.

Morphology

The lesions are flesh-coloured or yellow, soft, fleshy, smooth-domed papules or plaques that may become wrinkled or cerebriform with a *peau d'orange* texture (Fig. 8.28). Occasionally they are hairy and may contain comedones.

Distribution

Unilateral and usually on the lower back, buttocks, upper thighs or hips.

Histopathology

The lesion is characterized by the presence of mature fat cells within the superficial dermis (Fig. 8.29) and sometimes by abnormalities of connective tissue, blood vessels and appendages.

Management

If necessary and technically feasible, surgery is the treatment of choice.

Congenital smooth muscle naevi

Relatively common hamartomas of pilar smooth muscle.

Clinical Features

Symptoms

Usually present at birth or shortly thereafter as a single asymptomatic plaque.

Morphology

A poorly defined indurated skin coloured or faintly pink plaque (Fig. 8.30). Follicular papules may be seen on the surface. It varies in size from 1 to 10 cm.

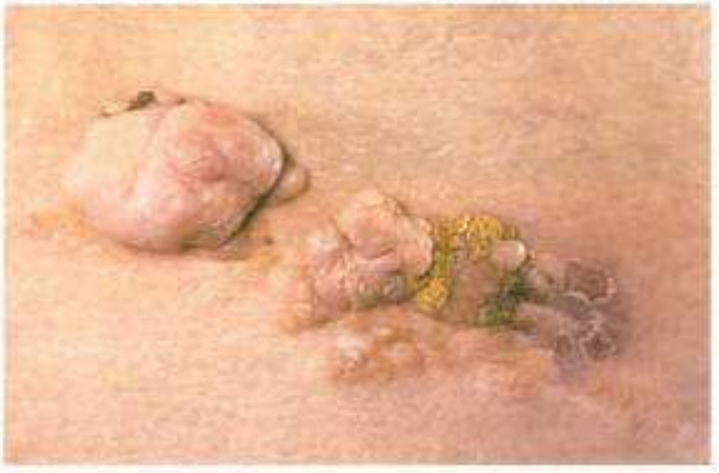


Fig. 8.28 Naevus lipomatosus superficialis. Multiple soft fleshy cerebriform papules and nodules are present. (Courtesy of the Institute of Dermatology.)

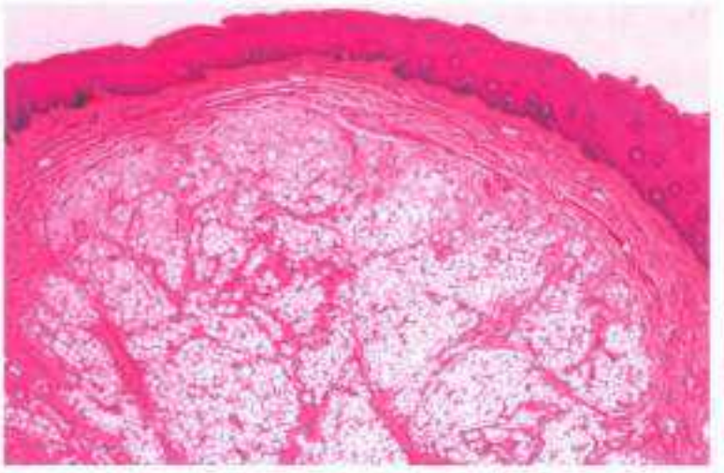


Fig. 8.29 Naevus lipomatosus superficialis. Lobules of mature adipose tissue are present high in the dermis. (Courtesy of Dr Jon Salisbury.)

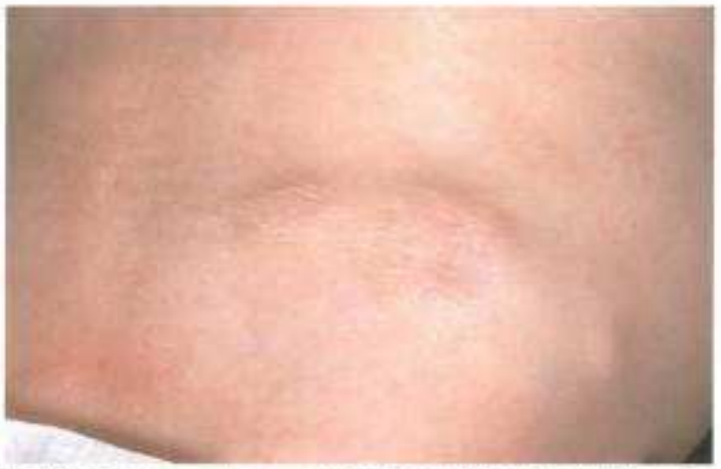


Fig. 8.30 Smooth muscle naevus. A single poorly defined indurated plaque of variable size is present at birth. (Courtesy of Dr D. Atherton and Dr S. Morris.)

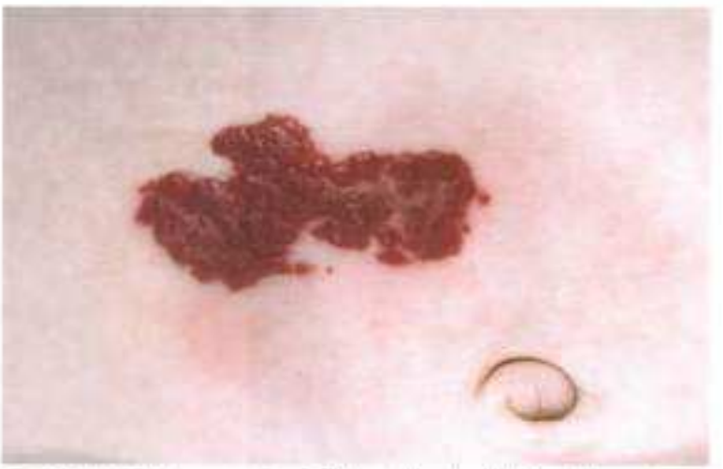


Fig. 8.31 Infantile haemangioma. The lesion here is a bright red plaque in a 2-month-old baby. It generally reaches its maximum size within the first 6 months. This is the proliferative phase.

Distribution

Congenital smooth muscle naevi are found on the trunk or limbs.

Histopathology

There are well-defined bundles or long straight smooth muscle fibres that extend in different directions and stain with Masson's trichrome.

Management

Congenital smooth muscle naevi are harmless and can be left alone. There is a very rare diffuse smooth muscle haematoma that has an identical histological appearance but the infant is born with excessive folding of rather firm skin on the limbs, particularly ankles and wrists, that have caused it to be known as the *'Michelin tyre baby'*.

Congenital vascular anomalies

Mulliken and Glowacki classified vascular anomalies into haemangiomas and vascular malformations. Haemangiomas have a cycle of growth followed by spontaneous regression. Vascular malformations may be subdivided into slow flow (capillary, lymphatic and venous malformations either alone or in combination) and fast flow (arterial malformations [Ch. 23], e.g. aneurysms and arteriovenous malformations) although there may be some overlap.

INFANTILE HAEMANGIOMA

Infantile haemangiomas are rapidly growing, benign proliferations of endothelial cells. They attain quite sizeable proportions but usually gradually resolve over the next few years.

Aetiology

The prevalence is about 1%. One-fifth are present at birth. The rest appear shortly thereafter. They are slightly more common in the premature, and presumably represent an abnormality of embryonic angioblastic development.

Clinical Features

Symptoms

An asymptomatic rapidly growing, usually red lump.

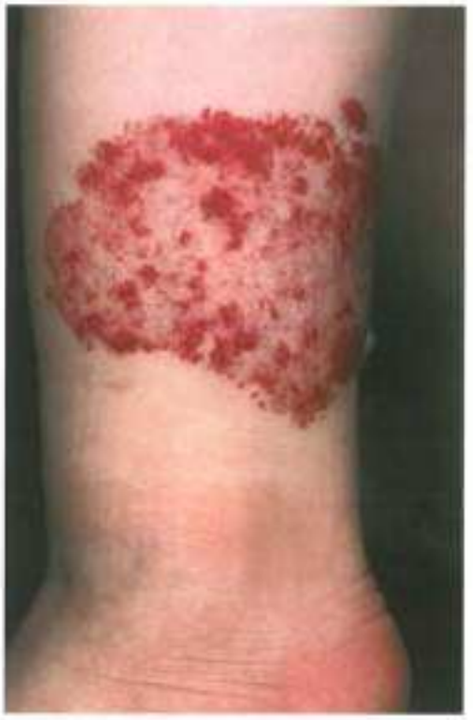


Fig. 8.32 Infantile hemangioma. The lesion gradually resolves and the deep red colour fades and the normal flesh tones become evident as in this 1 year old.

Morphology

A sharply circumscribed, bright red (Fig. 8.31), crimson or purple rounded dome-shaped tumour with a smooth lobulated and sometimes partially eroded surface. This superficial form, which involves the papillary dermis, is sometimes known as a strawberry naevus. They may be solitary or multiple. The colour deepens during the first year of life and the lesion reaches its maximum size, which varies greatly, within the first 6 months (proliferative phase). They gradually resolve (Fig. 8.32) completely in most

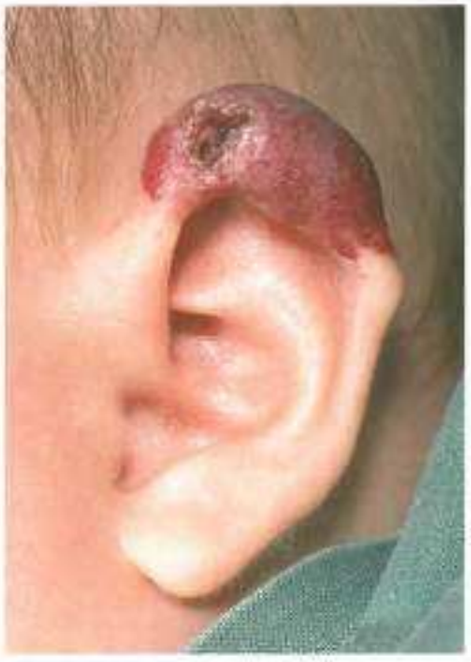


Fig. 8.33 Infantile haemangioma.
The lesion grows rapidly but is asymptomatic unless it bleeds, becomes infected or obstructs a vital structure.

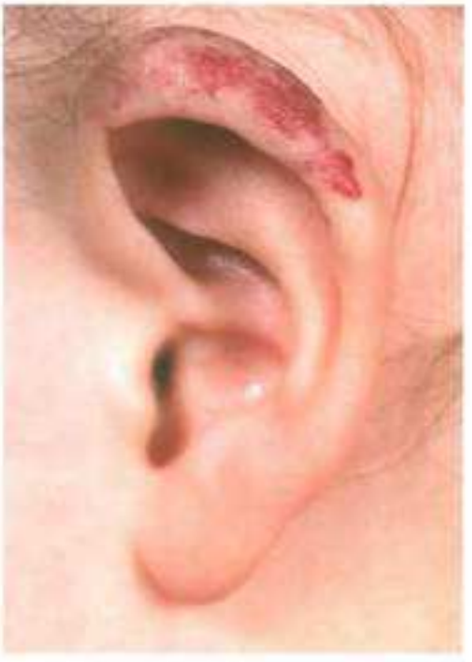


Fig. 8.34 Infantile haemangioma. Most superficial haemangiomas resolve completely within the first 7 years of life and require no treatment. Laser therapy is indicated in certain circumstances. This is the same patient as in Fig. 8.33.

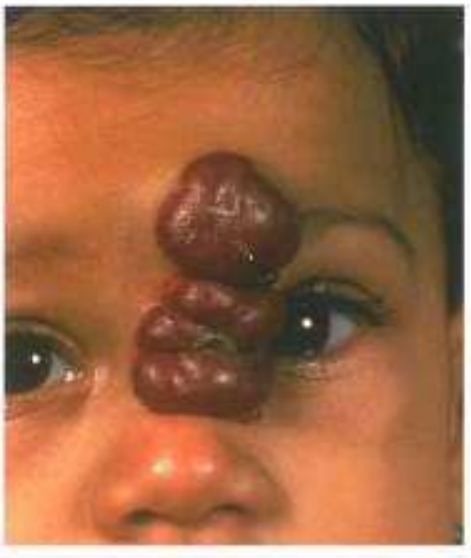


Fig. 8.35 Infantile haemangioma.
The naevus appears shortly after birth and is red and raised. Lesions on the face are a great trial to the parents, whereas the child is oblivious until older, by which time most naevi begin to show signs of resolution.

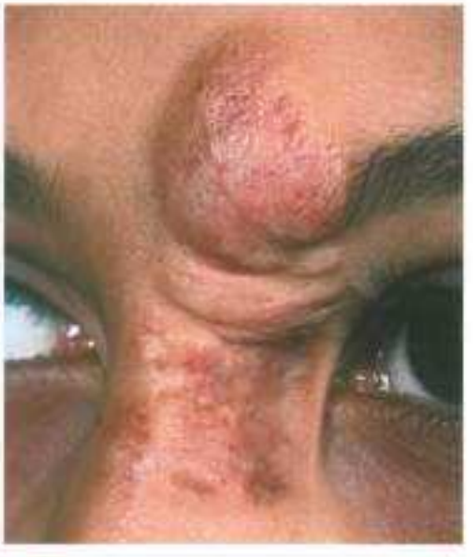


Fig. 8.36 Infantile haemangioma. This is the same patient as in Fig. 8.35 at the age of 9. The strawberry naevus has displaced the normal dermal architecture and resulted in abnormal cutaneous laxity requiring surgical revision.

cases (Figs 8.33 and 8.34) but they can displace the normal dermal architecture (like a tissue expander) resulting in abnormal cutaneous laxity (Figs 8.35 and 8.36). Deeper lesions that involve the reticular dermis and subcutaneous fat, and which used to be known as cavernous haemangiomas, are subcutaneous nodules with a blue or normal colour.

Distribution

The head (Fig. 8.35) and neck are the most common sites for these haemangiomas, then the trunk and limbs.

Histopathology

The early proliferative lesion is highly cellular with plump endothelial cells (Fig. 8.37) that lie in vascular spaces with small inconspicuous lumina. As the lesion matures, the endothelium flattens and the lumina appear more obvious and larger and, thus, cavernous in morphology. With regression, there is interstitial fibrosis with adipose metaplasia.

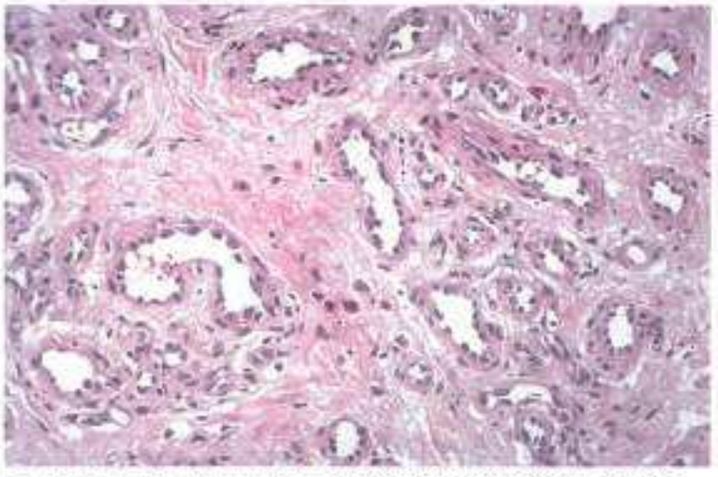


Fig. 8.37 Infantile haemangioma. The vascular channels are lined by plump endothelial cells. Mast cells with eosinophilic cytoplasm are scattered throughout the tumour.

Complications

- **Bleeding** Occasionally the lesion bleeds, although this usually responds to simple pressure. The surface of the haemangioma may erode but this is, on the whole, of no significance.
- **Infection** Occasionally secondary infection with septicaemia, especially with group A streptococci, is associated with ulceration.
- **Obstruction** The location of the haemangioma is important. Those surrounding the eye may cause amblyopia and raised intraocular pressure. Those around the nose, mouth, upper airway and ear may impair function by obstructing the airway, interfering with feeding or with the development of binocular vision.
- **Vascular abnormalities** Large diffuse facial lesions may be associated with major blood vessel abnormalities including coarctation of the aorta and abnormalities of the posterior fossa.
- **Visceral haemangiomas** Multiple haemangiomas may be accompanied by visceral haemangiomas, and most organs have been described as being involved. If this is extensive, there is an appreciable mortality because of high-output congestive cardiac failure.
- **Kasabach–Merritt syndrome** This is a vascular proliferation associated with decreased levels of circulating platelets and clotting factors caused by primary activation of platelets that adhere to the endothelial walls of the vascular channels of the tumour. This aggregation of platelets may be associated with secondary consumption of clotting factors, consistent with a localized intravascular coagulation.

Management

Diagnosis is usually not in doubt. Infantile haemangiomas should be distinguished from vascular malformations, which are warm, soft, easily compressible and fully developed at birth. They expand commensurate with the infant's growth and the colour persists. Masterly inactivity is all that is usually required for most because 30% of strawberry naevi are gone by the third birthday, 50% by the fifth and 70% by the seventh. Even deep lesions resolve completely in most cases but a few, although resolving considerably, do leave some residual disfigurement in terms of redundant skin, which can be excised at a later date. Serial photographs to illustrate the ultimate resolution of the problem in other children are very useful.

Obstructive lesions may need to be treated with intralesional systemic steroids. Multiple haemangiomas should be investigated with ultrasound or magnetic resonance imaging for the presence of other organ involvement. If there is any evidence of a high cardiac output state or the Kasabach–Merritt syndrome (when a subcutaneous haemangioma becomes hard and tender and bleeds) urgent referral to a hospital is indicated.

Laser therapy is being used to treat haemangiomas, particularly, for example, lesions on the nose where resolution may be slow. Surgery or X-ray irradiation should be firmly resisted. Systemic steroids are given more complicated haemangiomas but propranolol over several months is now the treatment of choice.

VASCULAR MALFORMATIONS

Capillary Malformations

Capillary malformations occur as port wine stains or telangiectasias. Port wine stains may be present as a solitary feature or be part of a syndrome. Telangiectasias similarly may occur alone (angioma serpiginosum and cutis marmorata) or as part of a syndrome (hereditary haemorrhagic telangiectasia and ataxia telangiectasia).

PORT WINE STAIN (NAEVUS FLAMMEUS)

A permanent vascular malformation that is present at birth and is a serious cosmetic disability especially if it occurs on the face. It is occasionally associated with congenital glaucoma, intracranial angiomas (Sturge–Weber syndrome), limb hypertrophy (Klippel–Trenaunay–Weber syndrome) and other syndromes.

Clinical Features

Symptoms

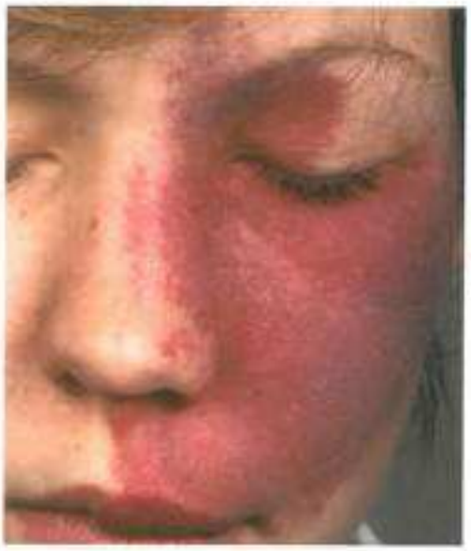
A purple patch, present at birth.

Morphology

The lesion is completely flat initially but may become raised (cobblestoned) and darker later in life. It is usually purple (Fig. 8.38) and is a permanent stain that varies in size from a few to several centimetres.

Distribution

It is usually unilateral and can occur anywhere, but particularly on the nape of the neck and the face (Fig. 8.39). On the face, the lesion frequently covers the distribution approximating to the sensory branches of the trigeminal nerve. Port wine stains on the limbs and trunk may eventually fade away.



Figs 8.38 Port wine stain. There is usually a unilateral purple patch initially (often in the distribution of the trigeminal nerve), which may become darker and cobblestoned later in life. Glaucoma and other ocular problems occur, particularly in association with lesions near the eye.

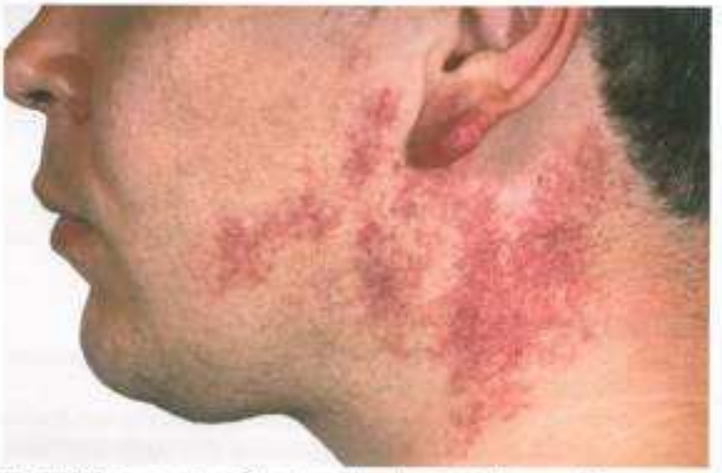


Fig. 8.39 Port wine stain. The rich purple colour gives it its name. It is permanent but laser therapy may be helpful in a case such as this.

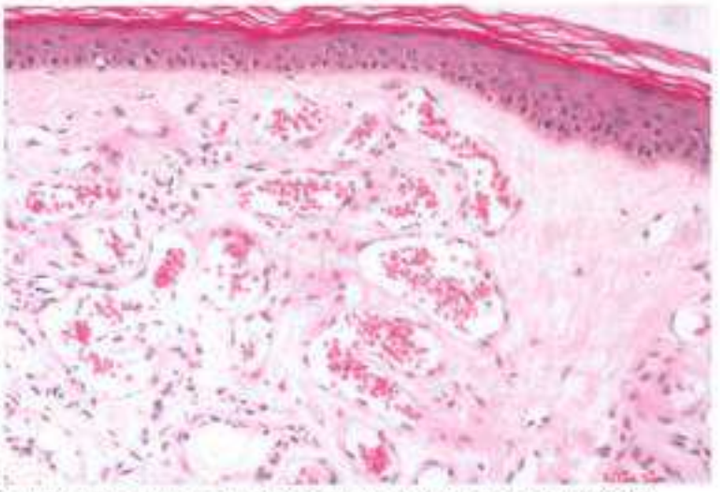


Fig. 8.40 Port wine stain. The lesion is characterized by numerous dilated thin-walled capillaries.

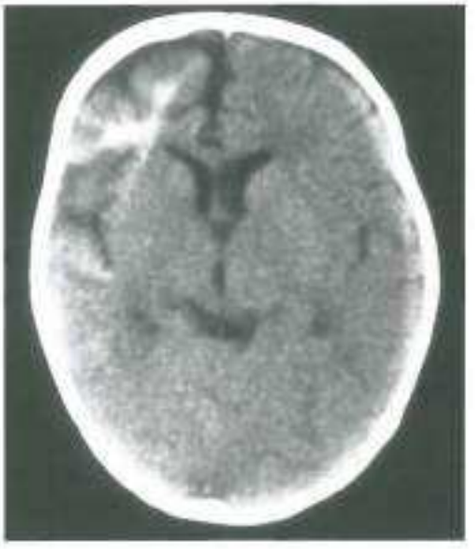


Fig. 8.41 Sturge–Weber syndrome. Epilepsy, mental retardation and contralateral hemiparesis may occur. Gyral calcification and underlying cortical atrophy is present. (Courtesy of Dr P. Gishen, King's College Hospital.)

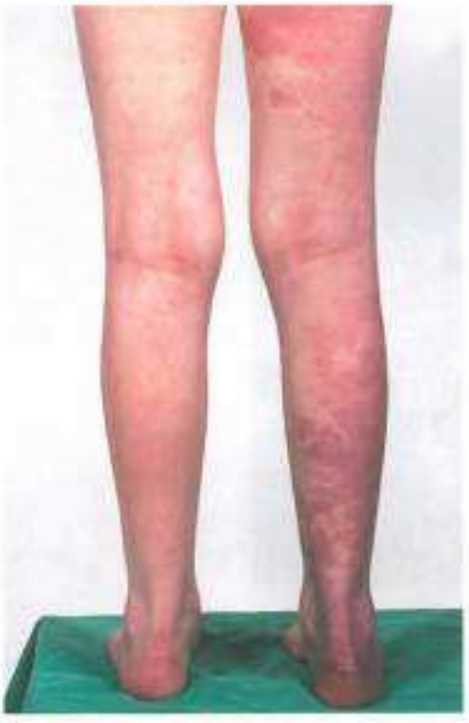


Fig. 8.42 Klippel–Trenaunay–Weber syndrome. This is a triad of venous varicosities, a port wine stain along one limb and overgrowth of the subcutaneous tissues and bone.

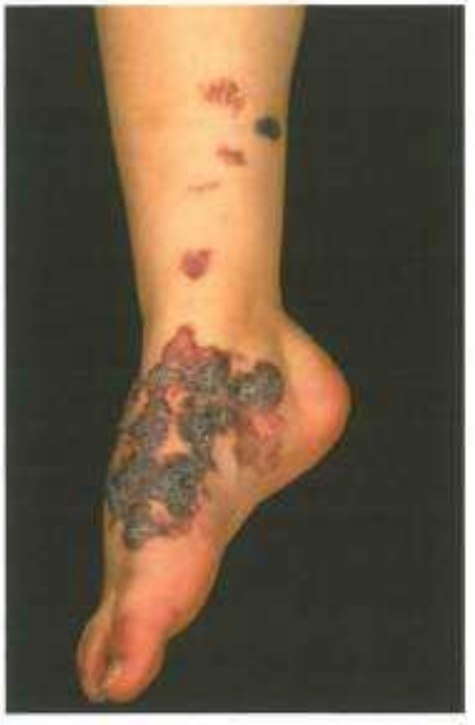


Fig. 8.43 Klippel–Trenaunay–Weber syndrome. There are blebs and hyperkeratosis depicted here, indicating additional lymphatic involvement. There are also angiokeratomas.

Histopathology

There is progressive ectasia of the superficial dermal capillaries that gradually involves the deeper vessels. There are widespread dilated blood-filled vascular channels that show no proliferative features (Fig. 8.40).

Complications

Most of these patients are perfectly well in every other respect, although the lesion is disfiguring and causes psychological hardship.

- **Glaucoma** This occurs in about 10% of patients especially with lesions on the upper lid. Lower lid stains are associated with ocular anomalies.
- **Sturge–Weber syndrome** Intracranial angiomas may occur in association with vascular naevi that involve the distribution of the trigeminal nerve. The conjunctivae and oral mucosa are often affected. The condition may present with epilepsy, mental retardation or contralateral hemiparesis. Radiography of the skull may reveal streaks of calcification in the angioma on the same side as the naevus, but not until at least 2 years of age. MRI with enhancement detects ocular and leptomeningeal vascular malformations early. Computed axial tomography and MRI have greatly improved the diagnosis and management of intracranial angiomas (Fig. 8.41).
- **Klippel–Trenaunay–Weber syndrome** This classically is a triad of a port wine stain extending down the limb, overgrowth of all the underlying tissues including bone and venous varicosities and/or venous malformations including persistence of embryological veins (Fig. 8.42). It is a capillary, lymphatic (Fig. 8.43) and venous malformation due to a defect of angiogenic factor VG5q. The stain may range in colour from

Fig. 8.44 Phakomatosis pigmentovascularis. There is a port wine stain with dermal melanocytosis. This is the type IIa variant.

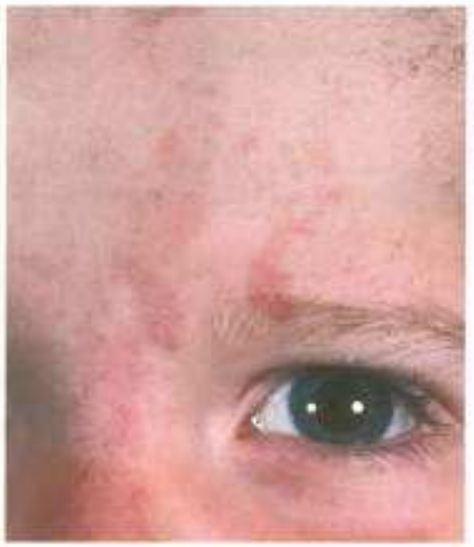


Fig. 8.45 Salmon patch. These pale pink patches are probably inherited as an autosomal dominant trait; they are present at birth, especially on the forehead, but fade within 1 year.

pink to deep red and may be associated with small angiomas or angiokeratomas. Geographic darker stains are a predictor for lymphatic complications. They often develop lymphatic blebs especially around the knee and lateral aspects of the leg. About half do gradually fade. The port wine stain is present at birth, although occasionally it may be absent altogether in the syndrome. The overgrowth of the underlying soft tissue and bones results in hypertrophy of the affected limb and a compensatory scoliosis. There may be hyperhidrosis or vasoconstriction from sympathetic overactivity. Venous lesions may occur in the bladder and gastrointestinal tract and there are often other non-cutaneous defects such as poly-, syn- or oligodactyly. Venous varicosities develop later in life and are often painful and may bleed quite extensively. Thrombophlebitis, cellulitis, stasis dermatitis and ulceration may occur. There is an increased incidence of deep vein thrombosis and pulmonary embolism. Verrucas are common. Sturge–Weber syndrome may occur in association with the Klippel–Trenaunay–Weber syndrome. Limb hypertrophy and port wine stains may occur in the Proteus syndrome but linear verrucous epidermal naevi, lymphangiomas, soft subcutaneous masses and other abnormalities are also present. In the *Parkes–Weber syndrome* the limb hypertrophy is caused by multiple arteriovenous fistulae and as a result, the skin is warm and pulsations may be felt and a bruit is audible.

- **Phakomatosis pigmentovascularis** This is a distinctive association of capillary malformations with melanocytic or epidermal naevi (Fig. 8.44). They have been classified as type I (port wine stain and linear epidermal nevus), type II (port wine stain, dermal melanocytosis and sometimes naevus anaemicus), type III (port wine stain, naevus spilus and sometimes naevus anaemicus) and type IV (port wine stain, naevus spilus and naevus anaemicus). They are further subdivided into (a) cutaneous involvement only or (b) extracutaneous presence of particularly intracranial abnormalities.
- **Cobb's syndrome** This is a segmental port wine stain occurring on the nape of the neck, or over the dorsal or lumbar sacral spine with an occult vascular malformation of the spinal cord at the same level.

Management

The diagnosis is not difficult. *Salmon patches*, which are extremely common, are a much paler pink in colour, occur most often on the forehead, glabella (Fig. 8.45), upper eyelids and lips and, although present at birth, fade within the first year.

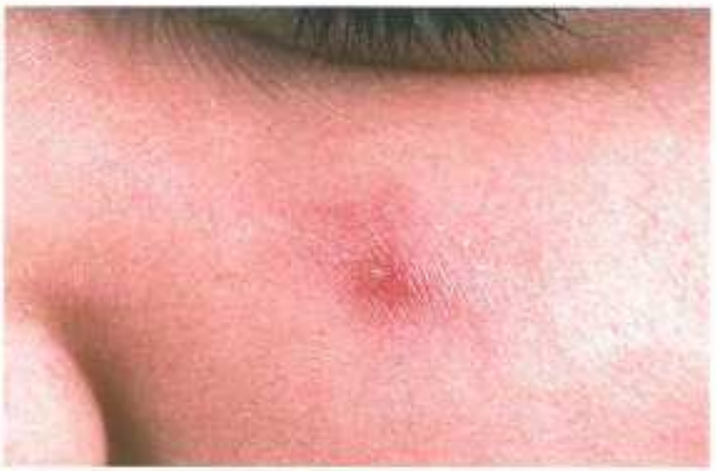


Fig. 8.46 Spider naevus. The lesion is common in childhood. It appears as a red compressible papule with fine vessels radiating outward from it.

Surgery, cryotherapy, thorium X, grenz rays and tattooing have been used but the argon laser is helpful, particularly in the darker, well-established lesions. Multidetector computer tomography scanners and fast three-dimensional magnetic resonance angiographic techniques are used to demonstrate the anatomy for therapeutic planning.

SPIDER NAEVUS

The spider naevus is a localized arterial dilatation of the skin.

Aetiology

The spider naevus arises spontaneously, usually in childhood or early adult life. Many appear during pregnancy and then spontaneously disappear; they may be precipitated by the use of oestrogens. Multiple and giant lesions are common associations of liver disease.

Clinical Features

Symptoms

An asymptomatic red blemish (Fig. 8.46).

Morphology

There is a central dilated red blood vessel from which tiny linear channels radiate outwards (Fig. 8.47).

Distribution

It may be single or multiple anywhere on the skin in the distribution of the superior vena cava. The face, upper chest and backs of the hands are the most common sites.

Management

The lesion is simple to treat. The central arteriole is obliterated with a cold cautery needle and then cauterized. There is barely any discomfort. A small scab forms which disappears within a few days. They often recur, but treatment can be repeated. Laser treatment is also effective.

VENOUS MALFORMATIONS

These are present from birth, grow proportionately during infancy and childhood but less so in adult life. Most are asymptomatic but some are swollen and painful. Extensive lesions may be associated with painful thrombotic episodes and localized intravascular coagulopathy with consumption of coagulation factors, anticoagulant effects of fibrin degradation products and exhaustion of hyperactivated platelets, especially following surgery or trauma. It may progress to disseminated intravascular coagulation. 1–2% are familial and linked to TIE2/TEK gain of function mutations on 9p21-22. The TIE2 signalling pathway is critical for endothelial cell–smooth muscle communication in venous morphogenesis. The lesions are a distinctive blue colour (Fig. 8.48) due to permeation of the papillary dermis by the abnormal venous network. Skeletal muscle and mucosae may be involved.

They may be cephalic (and penetrate deeper structures causing misalignment) involving the face and mouth (Fig. 8.49), trunk or limbs (Fig 8.50) (which may often lead to osteoporosis) and are often mistaken for KTS.

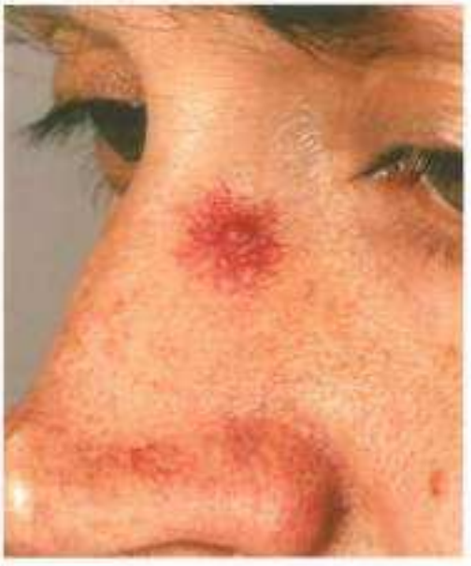


Fig. 8.47 Spider naevus. There is a central arteriole with tiny radiating linear channels. It is common in youth, pregnancy and may be a manifestation (usually giant and multiple) of liver disease.

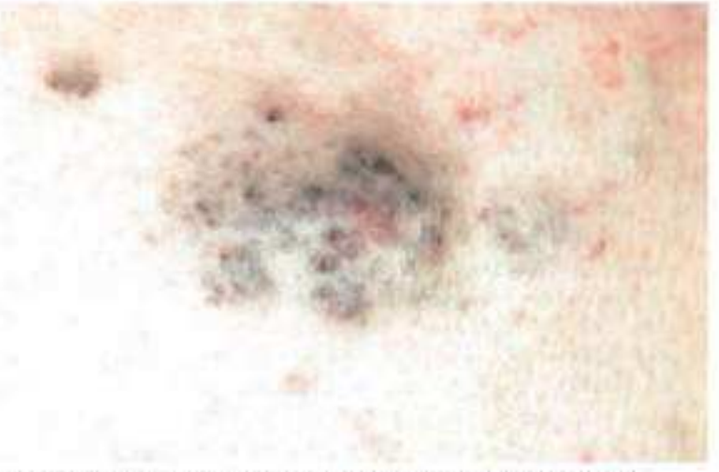


Fig. 8.48 Venous malformation. The lesions are soft, compressible, non-pulsating and swell and deflate with position. They have a distinctive blue colour.

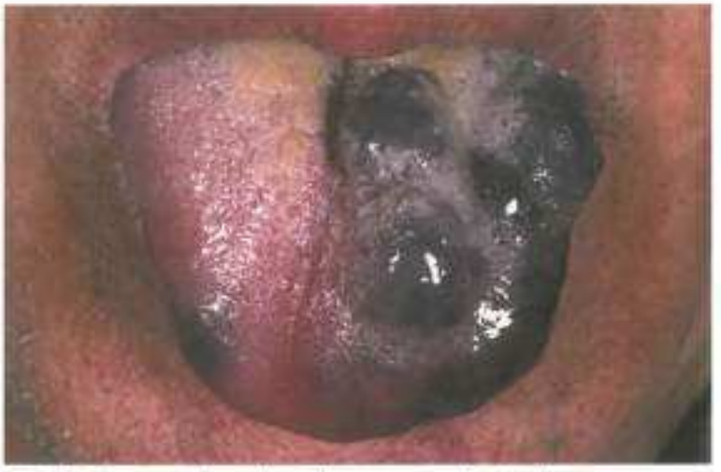


Fig. 8.49 Venous malformation. These are present from birth, grow proportionately during infancy and childhood but less so in adult life. They are disfiguring and some are painful.

Fig. 8.50 Venous malformation. The limbs are often involved and may be mistaken for Klippel–Trenaunay–Weber syndrome. Extensive lesions may be associated with painful thromboses and localized intravascular coagulation.

They begin in infancy as a bluish macular stain but enlarge and thicken with age. They are soft, compressible, non-pulsating and swell and deflate with position. They are occasionally painful, especially on waking, with cold or exertion. They are twice as common in women.

Telangiectasias

These are dilated anomalies of capillaries and may occur as angioma serpiginosum or cutis marmorata telangiectasia congenita or part of a syndrome, viz. hereditary haemorrhagic telangiectasia or ataxia-telangiectasia (Ch. 20).

ANGIOMA SERPIGINOSUM

A rare unilateral disorder of the superficial blood vessels affecting a limb or buttock, usually commencing in childhood in females.

Clinical Features

Symptoms

Asymptomatic eruption of minute red spots that appear in childhood and gradually extend for a year or more. In adult life it may grow further or remit completely or partially.

Morphology

Very small, red or purple punctate macules (Fig. 8.51) that do not blanch on pressure. There is usually a background of diffuse erythema.

Distribution

Along a limb (Fig. 8.52) or buttocks (Fig. 8.53) in a serpiginous or gyrate pattern.

Histopathology

The lesion is a proliferation of endothelial cells with formation of new capillaries rather than a dilatation of pre-existing capillaries. It is therefore more of a benign vascular neoplasm than a naevus. There are clusters of relatively thick-walled capillaries in the dermal papillae and there is no inflammatory infiltrate.

Management

Treatment is unsatisfactory.

Fig. 8.52 Angioma serpiginosum. The condition is uncommon, affects females predominantly and occurs in a serpiginous pattern along a limb or buttock. It may be more extensive. (Courtesy of Dr Michèle Clemant.)

CUTIS MARMORATA TELANGIECTATICA CONGENITA

A reticulate vascular naevus that is present at birth and composed of mixed capillary and venous dilations and lakes.

Aetiology

It occurs in approximately 1 in 3000 births. It is usually sporadic although occasionally familial. There is a relatively high incidence of other abnormalities, including underlying atrophy of the subcutaneous tissue with, for example, facial hemiatrophy, reduced girth of the affected limbs and hypoplasia of underlying bone.

Clinical Features

Symptoms

The abnormality is present at birth.

Fig. 8.51 Angioma serpiginosum. The individual lesions are minute red or purple punctate macules on a background of erythema.

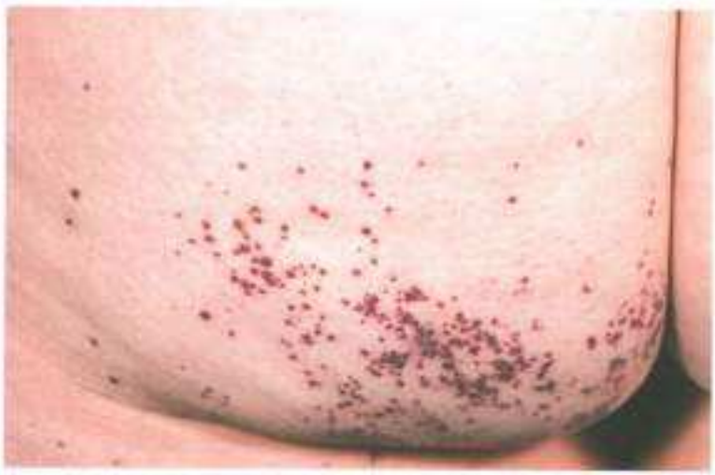


Fig. 8.53 Angioma serpiginosum. The lesion affects females and occurs early in life. There are clusters of small deep red or purple puncta often distributed unilaterally.

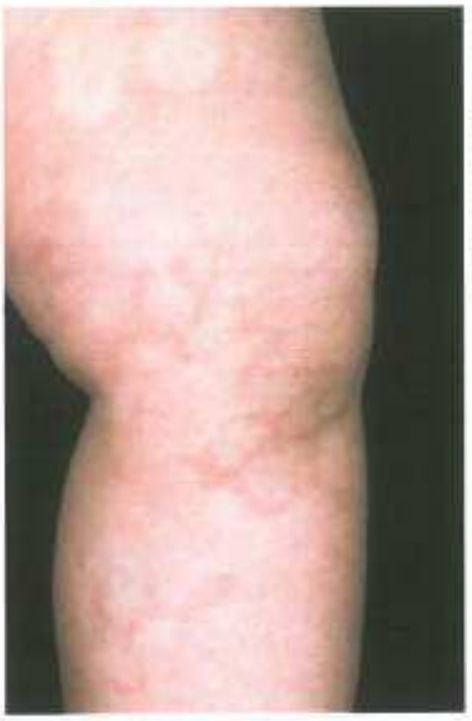


Fig. 8.54 Cutis marmorata telangiectatica congenita. There is a net-like erythema (note the blanching caused by finger tip pressure at the top of the figure) which is usually present at birth. One limb may be involved as here or it may be more extensive.

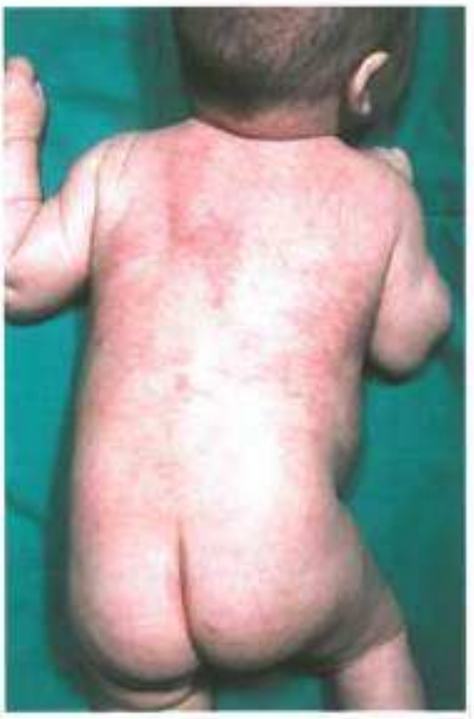


Fig. 8.55 Cutis marmorata telangiectatica congenita. There is a reticulated erythema, which may be associated with atrophy of the underlying subcutaneous tissue. If there are terminal limb anomalies and aplasia cutis it is known as Adams–Oliver syndrome.

Morphology
There is a reticulate erythema (Fig. 8.54) that is flat or depressed, producing a striking appearance. It ranges from pale red to a deep purple colour and telangiectasia may be evident within the hyperaemia; the skin may be atrophic and even eroded.

Distribution
The involvement may be limited or extensive (Fig. 8.55): one limb may be involved or most of the body.

Histopathology
Dilated capillaries and veins are found throughout the dermis and often subcutis, and capillary and venous lakes may be formed.

Management
The diagnosis is not difficult and it can be distinguished from the physiological reaction to cold known as *cutis marmorata*, which disappears with warmth, and also the congenital livedos associated with Down's syndrome and homocystinuria. Many of the lesions fade with time and so active treatment with lasers is not usually necessary.

Angiokeratomas

Pathologically there is dermal capillary ectasia with an acanthotic and hyperkeratotic epidermis. They occur more commonly either singly or as multiple lesions on the vulva or scrotum (Ch. 9). They may present at birth as a plaque or linear lesion on a limb (angiokeratoma circumscriptum) or on the extremities (angiokeratoma of Mibelli) or as part of an X-linked recessive deficiency of α-galactosidase A (angiokeratoma corporis diffusum).

ANGIOKERATOMA OF MIBELLI
A rare autosomal dominant condition affecting girls particularly, with keratotic angiomatous papules on acral sites and cold intolerance.

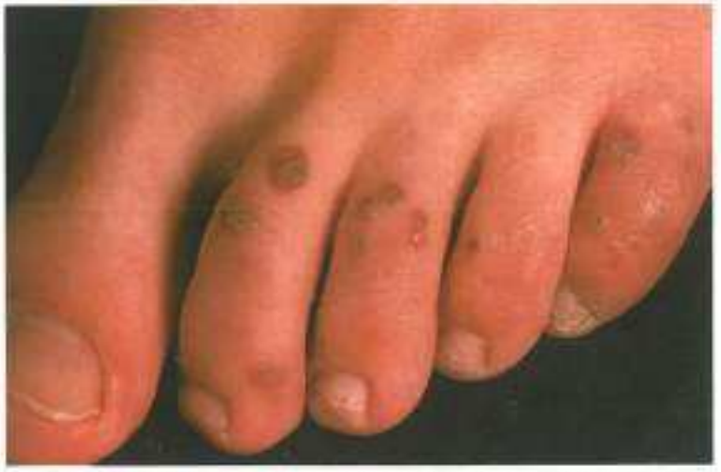


Fig. 8.56 Angiokeratoma of Mibelli. This rare autosomal dominant condition affects young girls and is associated with acrocyanosis and chilblains.

Clinical Features
Symptoms
Asymptomatic papules with painful acrocyanosis and chilblains.

Morphology
Initially minute, bright red macules which become warty, darker papules up to 1.5 cm in diameter (Fig. 8.56). They are persistent.

Distribution
The lesions arise most commonly on the sides and the backs of fingers and toes but also on the hands, feet, knees, elbows and buttocks.

Management
Keeping the extremities warm is important. Individual angiokeratoma lesions respond to cryotherapy, electrodessication or excision.

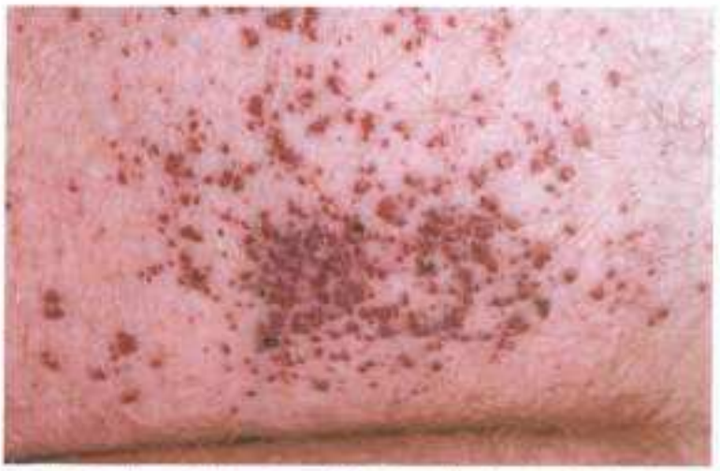


Fig. 8.57 Anderson–Fabry disease. Periodic attacks of excruciating burning pain and fever occur in association with a myriad of discrete purple papules. (Courtesy of Dr Robert Holmes.)

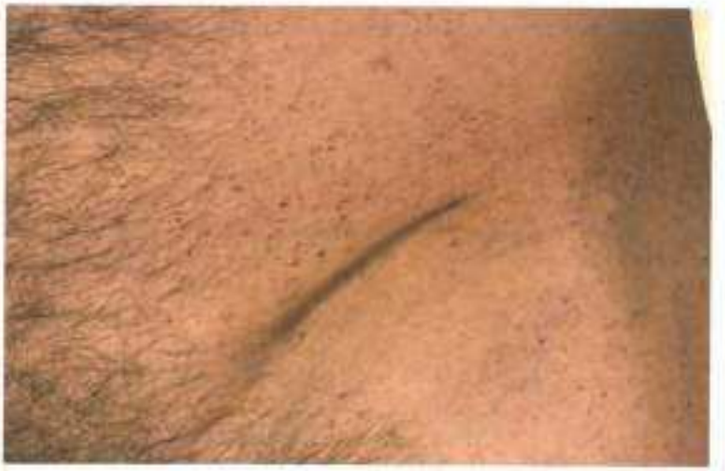


Fig. 8.58 Anderson–Fabry disease. The angiokeratomas occur particularly around the lower trunk, hips, thighs, buttocks and genitalia.

ANGIOKERATOMA CORPORIS DIFFUSUM

A rare X-linked recessive disorder of males caused by deficiency of α-galactosidase A, which leads to deposition of glycolipid in small blood vessels of the skin and viscera.

Aetiology

Anderson–Fabry disease (angiokeratoma corporis diffusum) is a disorder of sphingolipid metabolism. Patients have a deficiency of the lysosomal enzyme α-galactosidase A (ceramide trihexosidase). This results in an accumulation of the glycolipid ceramide trihexoside within the cytoplasm of cells of a variety of tissues, including blood vessels, smooth muscle, heart, kidney, bowel, eye and central nervous system.

A similar cutaneous eruption is also characteristic of several rare inherited lysosomal disorders of which Anderson–Fabry disease is the best known. The others manifesting deficiencies of enzymes involved in the metabolism of glycoproteins are fucidosis, sialidosis, mannosidosis, GM1 gangliosidosis and Kanzadi disease.

Clinical Features

Symptoms

Periodic attacks of excruciating burning pain in the extremities (acroparaesthesia) associated with fever are unexplained but virtually diagnostic symptoms of angiokeratoma corporis diffusum.

Morphology

The lesions are dark red or black telangiectatic macules or papules up to 0.5 cm across (Fig. 8.57), usually appearing just after puberty.

Distribution

The papules may be grouped and few in number, but usually they are diffuse, around the umbilicus, hips, buttocks, lower trunk (Fig. 8.58), genitalia and thighs.

Systemic features

The conjunctival and retinal vessels are dilated and tortuous and corneal opacities may be present, which may help to identify female carriers. A symptomless superficial corneal dystrophy (cornea verticillata) is virtually diagnostic. Vasomotor instability (blue or white peripheries and flushing of the extremities), hypohidrosis, lymphoedema and varicose veins are common. The facial features may be coarsened. Cardiomyopathy, renal failure and cerebral vascular accidents are serious complications.

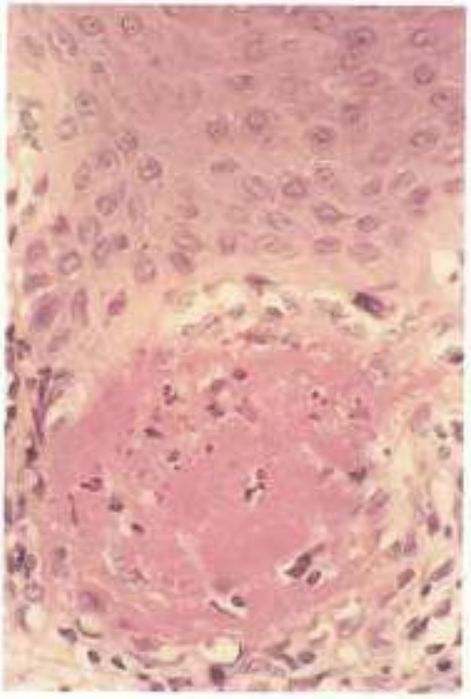


Fig. 8.59 Anderson–Fabry disease. Small vacuoles secondary to lipid deposition are found in the endothelial cells.

Histopathology

The lesions consist of dilated thin-walled blood vessels situated within the upper, particularly papillary, dermis, which often appear to be located within the epidermis. There is a variable degree of associated hyperkeratosis, as in other angiokeratomas. However, small vacuoles are found in the media of cutaneous blood vessels (Fig. 8.59) in Anderson–Fabry disease and are of diagnostic importance. Further vacuoles may be seen in endothelial cells and are strongly diastase-PAS positive. The deposits can also be stained on frozen sections using Sudan black. Similar vacuoles may be seen in the arrector pili muscles and smooth muscle elsewhere in the body, including the myocardium. Vacuolation of the renal glomeruli and tubular system is conspicuous, although at a later stage of the disease severe glomerulosclerosis is usually a feature. With electron microspcopy, characteristic lamellar bodies (periodicity 5 nm) and dense bodies (lipid inclusions) may be detected within the cytoplasm of endothelial and smooth muscle cells.

Management

Anderson–Fabry disease is a serious condition associated with a high mortality, especially in middle age. It primarily affects males but angiokeratomas of the skin may occur in heterozygote female carriers. Death is commonly from renal failure, but myocardial infarction and cerebrovascular accidents may also occur. Female carriers have a normal life expectancy. The diagnosis can usually be confirmed by a skin biopsy and eye examination. Alternatively, birefringent lipid-containing cells may be found in the urine (seen as Maltese cross-like structures under polarized light) and decreased α-galactosidase A levels may be detected in plasma leucocytes or cultured fibroblasts. It is due to replacement of asparaginase residues with serine at codon 215 (N215S) in the α GAL gene. There are over 200 mutations described. One-third of patients do not have angiokeratomas. There are variants with predominantly hypertrophic cardiomyopathy (N215AS mutation usually). Treatment has been revolutionized by enzyme replacement therapy (agalsidase α). Renal transplantation has been performed in patients with severe renal involvement.

NAEVUS ANAEMICUS

A circumscribed persistent patch of pale skin resulting from a pharmacological abnormality in which there is increased reactivity of blood vessels to catecholamines with no microscopic changes.

Aetiology

The lesion may be present at birth or commence in early childhood on the chest or limbs. It is persistent. The pallor is caused by an increased reactivity of the blood vessels to catecholamines and can be reversed by blocking the sympathetic nerves. There is a higher incidence in von Recklinghausen's disease and with port wine stains.

Clinical Features

Symptoms

An asymptomatic area of pale skin.

Morphology

There is a single well-defined area of pale skin (Fig. 8.60) with irregular margins that otherwise appears quite normal and is quite indistinguishable from the surrounding skin if blanched with a microscopic slide.

Distribution

Anywhere on the body.

Management

There is no effective treatment.

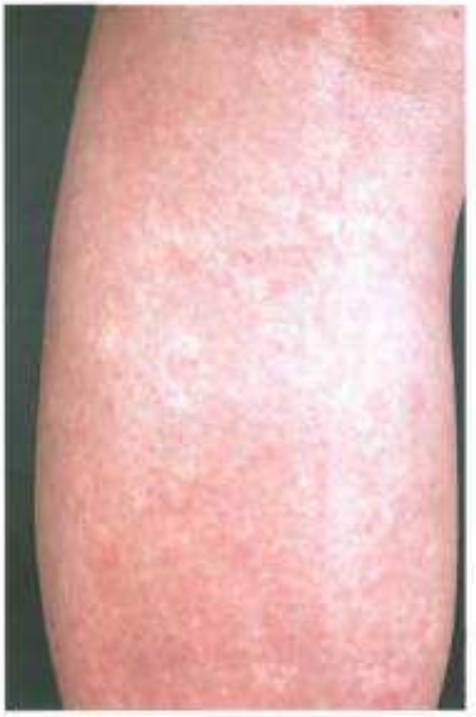


Fig. 8.60 Naevus anaemicus. The lesion is off-white, well defined and has irregular margins. It becomes indistinguishable from surrounding skin with pressure from a glass slide.

BLUE RUBBER BLEB NAEVUS SYNDROME

A rare sporadic or autosomal dominant syndrome of multiple venous malformations of the skin, gastrointestinal tract and other organs.

Clinical Features

Symptoms

Sometimes present at birth but usually appearing in early childhood, the lesions characteristically are spontaneously painful, particularly at night, especially after puberty and the skin overlying them may sweat.

Morphology

The lesions are generally quite small but may be large; they are compressible, soft, rubbery, blue or purple nodules (Fig. 8.61).

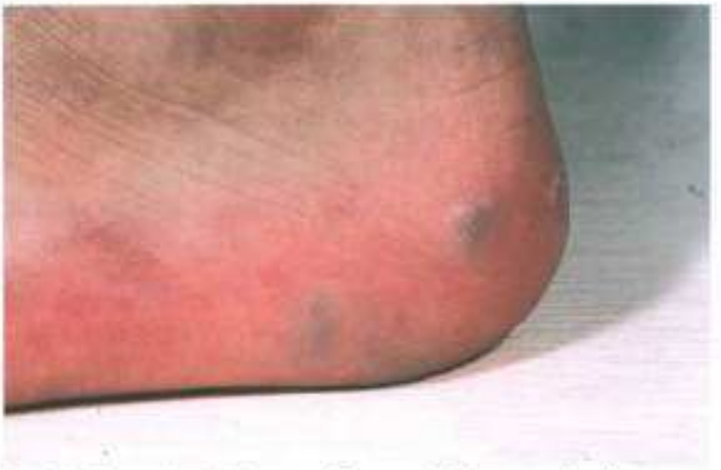


Fig. 8.61 Blue rubber bleb naevus. Compressible blue or purple rubbery or soft nodules occur anywhere on the skin. They are spontaneously painful, especially at night.

Distribution

They may occur anywhere including the genital or oral mucosa.

Histopathology

There are large blood-filled vascular lumina in the dermis and subcutaneous fat, which is separated by strands of connective tissue.

Management

The lesions are persistent. Destructive measures may be employed if necessary. The importance of the condition is the involvement of other organs and, particularly, bleeding from the gastrointestinal tract.

Lymphatic malformations

These may be microcystic (lymphangioma circumscriptum) or macrocystic (cystic hygromas). Some have complex combined vascular malformations, viz. capillary lymphatic, lymphatic venous or lymphatic arteriovenous. A few overlap with haemangiomas and vascular malformations, e.g. *Maffucci's syndrome*. It occurs sporadically. The infant is normal at birth but in early childhood multiple superficial and deep blue/purple soft, occasionally tender, nodules occur on the distal extremities with oral and intra-abdominal venous and lymphatic abnormalities associated with enchondromas of the phalanges and long bones, which may turn malignant (chondrosarcoma). It is also associated with breast, ovarian, pancreatic, parathyroid and pituitary cancer. Spindle cell haemangioendotheliomas of the skin are a specific finding.

LYMPHANGIOMA CIRCUMSCRIPTUM

It is usually present at birth as a cluster of vesicles on the buttocks or trunk caused by dilatation of thin-walled lymphatic channels.

Clinical Features

Symptoms

The patient frequently notices a clear fluid discharge.

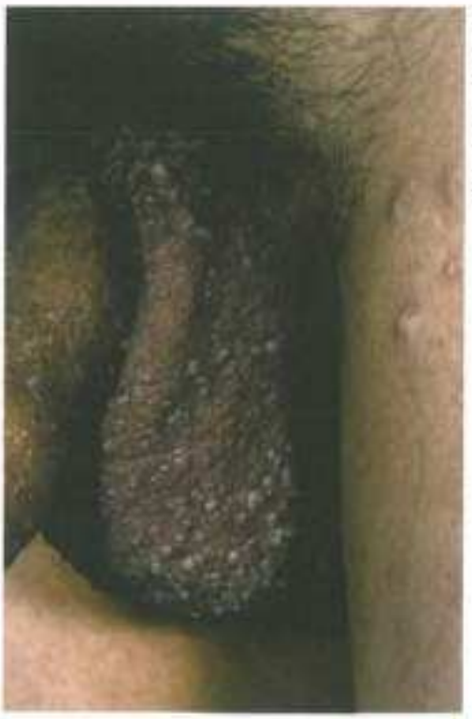


Fig. 8.63 Lymphangioma circumscriptum. There are discrete collections of fluid-filled vesicles. It is not uncommon for the genitalia to be affected.

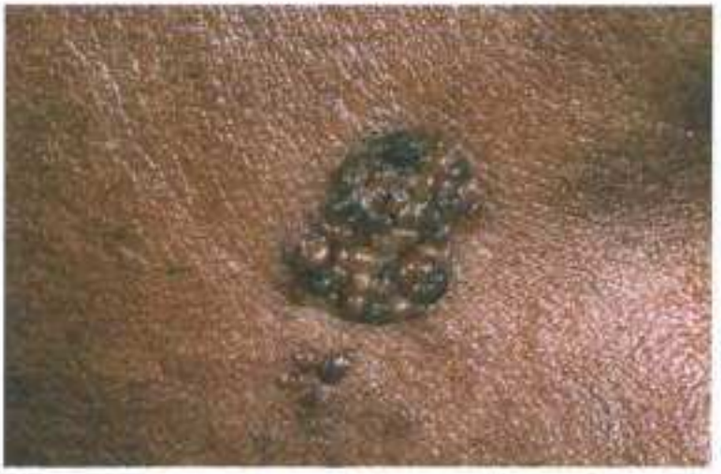


Fig. 8.62 Lymphangioma circumscriptum. A cluster of vesicles occurs from which clear fluid may discharge. The lesions are usually present at birth and may be associated with the Proteus or Maffucci's syndrome.

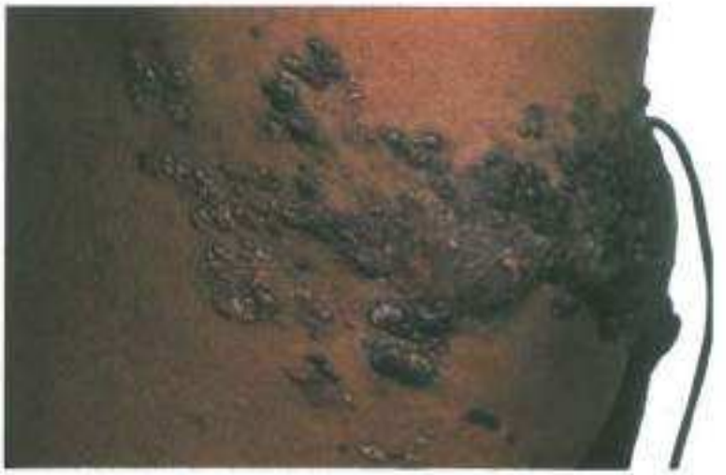


Fig. 8.64 Lymphangioma circumscriptum. The vesicles may discharge clear or haemorrhagic fluid. They are best left untreated at present.

Morphology

There are vesicles, arranged in clusters (Fig. 8.62), containing clear or haemorrhagic fluid, which occasionally becomes secondarily infected.

Distribution

The buttocks, genitalia (Fig. 8.63) or torso (Fig. 8.64) are the most common sites.

Management

The histopathology is of a collection of dilated, thin-walled lymphatic channels that very often contain lymph (Fig. 8.65). The surrounding epidermis is acanthotic. The lymphatic spaces within the papillary dermis may simulate an intraepidermal location. The lesions are best left alone. If

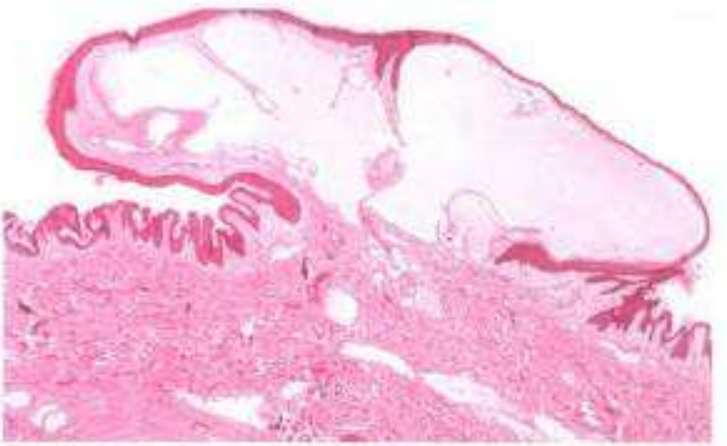


Fig. 8.65 Lymphangioma circumscriptum. This scanning view shows a polypoid lesion composed of greatly dilated lymphatic channels. Scattered smaller vessels are also present in the reticular dermis.

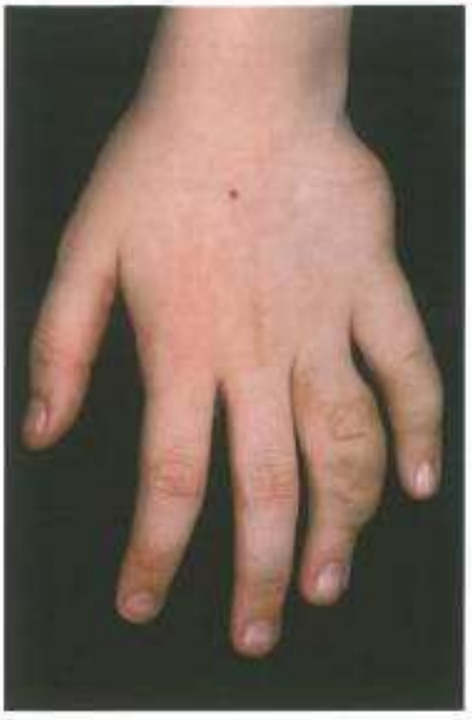


Fig. 8.66 Maffucci's syndrome. Bony nodules of dyschondroplasia occur in the fingers and toes, which causes fractures and deformities, in association with lymphangiomas and haemangiomas.

Fig. 8.67 Meningoencephalocoele. The vertex of the scalp is the classical site for failure of closure of the neural tube and thus encephalo- or meningomyelocoeles. The lesion is a red blue subcutaneous nodule. It requires imaging studies.

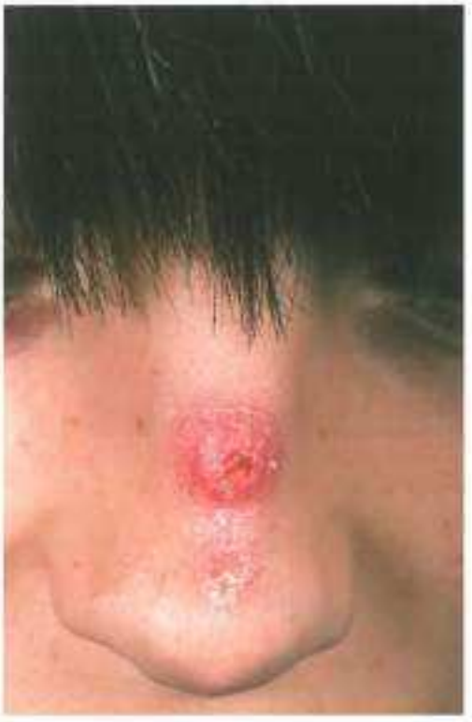


Fig. 8.68 Dermoid cyst. This is a squestration of ectoderm along embryological fusion lines. They are usually present at birth but may escape detection until they become inflamed. Midline nasal lesions may have intracranial extension.

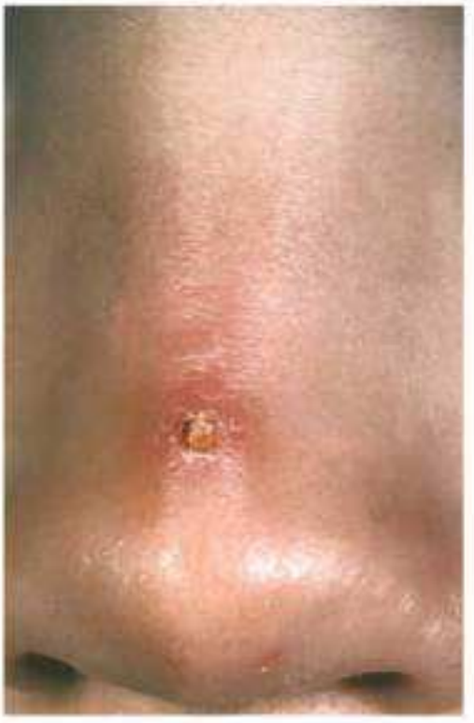


Fig. 8.69 Median nasal sinus. These midline lesions may have intracranial connections and are a risk for infection including meningitis and cerebral abscess.

they are excised they almost always recur. Magnetic resonance imaging demonstrates how extensive they are in the subcutis. Radiotherapy has been used. Lymphangiomas are seen in the Proteus and Maffucci's syndromes (Fig. 8.66).

Developmental defects

Anomalies may result from errors in embryological development (e.g. incomplete closure of the neural tube) or damage to a structure before it is fully formed (e.g constriction of a limb from an amniotic band). Although detailed description remains outside the scope of this text, recognition of certain serious presentations in the skin may prevent unwitting meddlesome intervention, particularly with lesions involving the midline. Congenital scalp lesions include *encephalocoeles* (Fig. 8.67). These are herniations of the meninges and brain, are present at birth and occur at the vertex or occiput. They may also be located at the nasal root or glabella. The differential diagnosis includes a *dermoid cyst* (Fig. 8.68) but a seemingly innocuous pit may represent a *dermal sinus* (Fig. 8.69) and result in recurrent episodes of meningitis. Midline lesions also occur in the neck including *thyroglossal cysts* (Fig. 8.70), sternum and spine. The latter is the

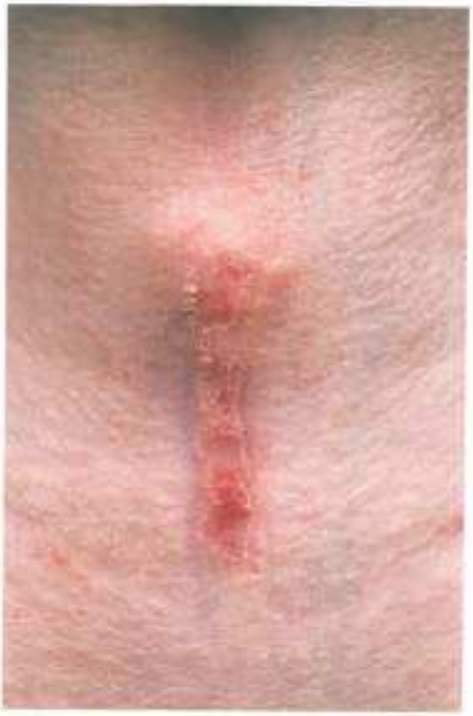


Fig. 8.70 Thyroglossal duct. These are present at birth. There is a vertical linear cleft along the midline of the neck covered with atrophic skin. There is a protuberance superiorly and a sinus tract inferiorly.

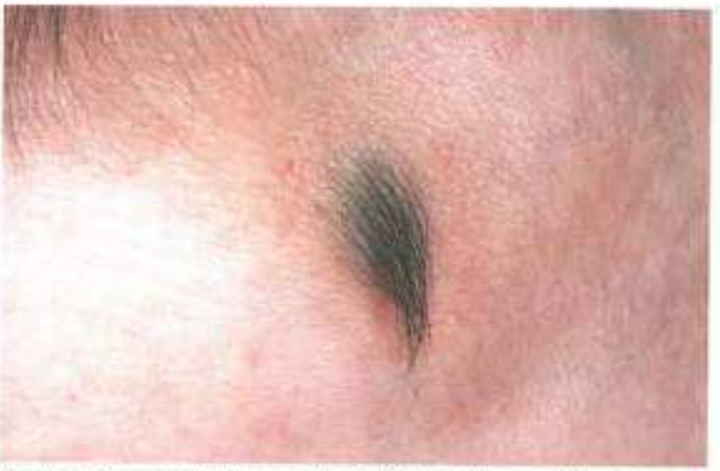


Fig. 8.71 Circumscribed hypertrichosis. Midline lumbar sacral long hairs ('faun tail') may represent spinal dysraphism (abnormal embryological dorsal fusion of the spine).

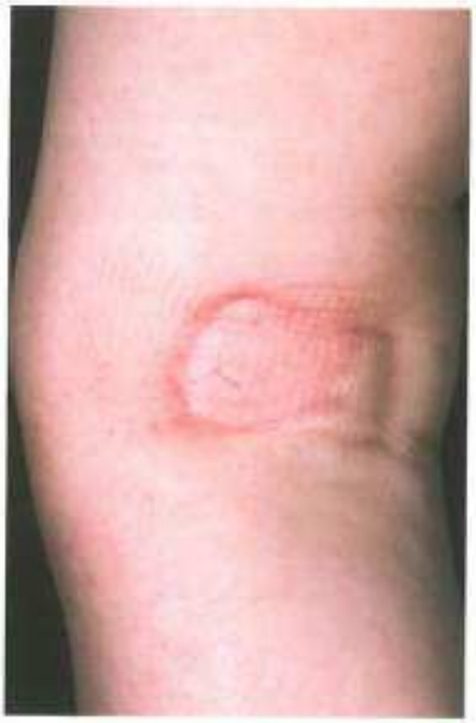


Fig. 8.72 Aplasia cutis. There is a discrete ovoid defect covered by a membrane as here, or an erosion or scar. There are several causes, including genetic, vascular, intrauterine viral infections and teratogens.

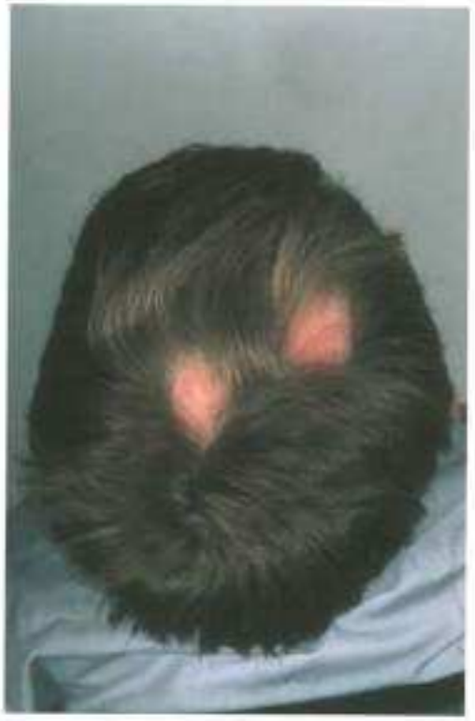


Fig. 8.73 Aplasia cutis. There is localized absence of the skin, usually at the vertex, at birth. In the scalp it may overlie a neural tube defect, be associated with other congenital anomalies, be part of the Adams–Oliver syndrome or be an isolated finding.

classic site for meningomyelocoeles. These lesions are obvious, but *occult spinal dysraphism* may present as a midline dimple, lipoma, circumscribed hypertrichosis (Fig. 8.71) ('faun tail') or haemangioma (Cobb's syndrome). Evaluation of these lesions by MRI is essential.

Aplasia cutis is a physical sign implying localized congenital absence (Fig. 8.72) or scarring of the skin. The commonest affected area is the scalp (Fig. 8.73) and it may present as an isolated defect, as part of the *Adam–Oliver syndrome* or associated with other congenital defects. It may also be secondary to ischaemia (particularly placental infarction or second trimester death of a twin), drugs (e.g. carbimazole and low molecular weight heparin), maternal antiphospholipid syndrome and intrauterine herpes simplex or varicella. It is seen in epidermolysis bullosa.

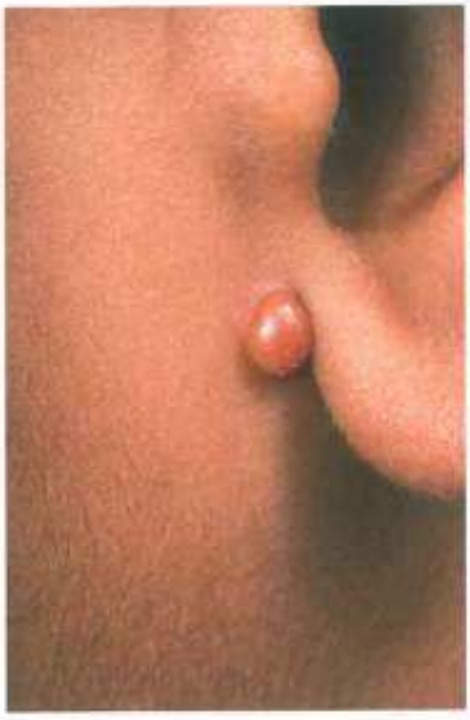


Fig. 8.74 Accessory tragus. These may occur in front of the ear, on the mandibular cheek or along the anterior border of the sternomastoid muscle. They are developmental anomalies of the first branchial arch and may be part of a syndrome (e.g. Treacher–Collins).

Fig. 8.75 Preauricular sinus and cyst. This results from imperfect fusion of the small tubercles of the first and second branchial arches. The pit immediately in front of the ear is the clue to the cause of the cyst.

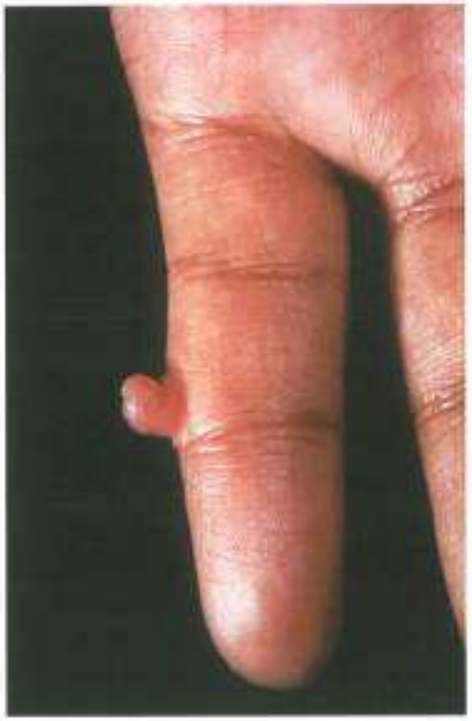


Fig. 8.76 Accessory digit. These are most common in the ulnar site of the fifth finger and are soft tissue rudimentary fingers without a bony component. They are present at birth and may be bilateral. Excision is the correct procedure if required.

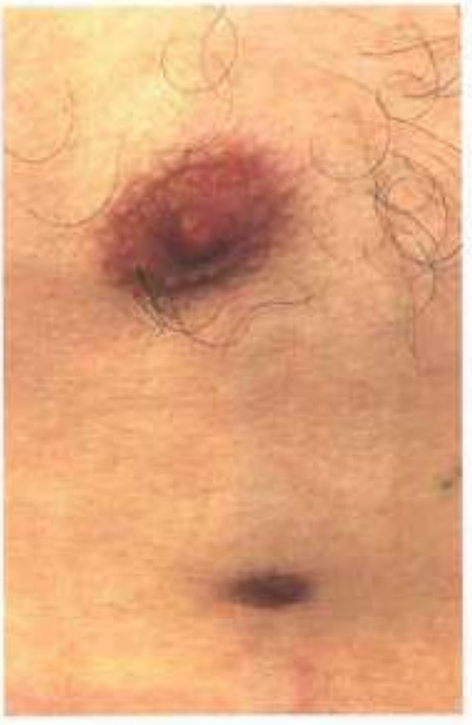


Fig. 8.77 Accessory nipple. A supernumerary nipple with its surrounding areola is present. These are embryological remnants of the mammary ridges which stretch from the anterior axillary fold to the upper inner thigh.

Non-midline developmental abnormalities tend to be less serious and include:

- accessory tragi (Fig. 8.74)
- preauricular sinuses and cyst (Fig. 8.75)
- rudimentary supernumerary digits (Fig. 8.76)
- accessory nipples (Fig. 8.77).

Benign tumours of the skin 9

Cutaneous cysts

A cyst is a closed cavity or sac containing fluid or semi-solid material with an epithelial, endothelial or membranous lining.

EPIDERMOID CYST

An epidermoid cyst is a cutaneous or subcutaneous cystic swelling of the skin, often with a central punctum, derived from squamous epithelium.

Aetiology

Most occur spontaneously (Fig. 9.1). Some are associated with acne (particularly nodulocystic), and are often inflamed (Fig. 9.2). They may also result from implantation of squamous epithelium following an injury.

Multiple epidermoid cysts occur in *Gardner's syndrome*, an autosomal dominant disorder, due to mutations in the APC (adenomatous polyposi coli) gene, a multi-function suppressor gene on 5q21. There are four phenotypes:

- Gardner's syndrome (epidermoid cysts)
- Turcot's syndrome (café-au-lait patches)
- Familial adenomatosis polypi
- Attenuated familial adenomatosis polypi.

Gardner's syndrome is associated with osteomas, fibromas and intestinal fibromatoses, lipomas, leiomas and adenomatous polyposis coli. 50% of patients develop polyps by 20 years of age; half of these polyps become malignant. Osteomas are found in the maxilla, mandible, sphenoid and occasionally the skull. They are small and multiple and may be identified radiologically. There is variable expressivity of the gene but most patients have congenital hypertrophy of the retinal pigment epithelium, which may be present before other manifestations have developed. These multiple bilateral pigmented lesions of the ocular fundus are a characteristic feature. There may be supernumerary teeth, dentigerous cysts and caries.

Clinical Features

Symptoms

The swelling of an epidermoid cyst is usually asymptomatic.

Morphology

A smooth mobile, dome-shaped cutaneous or subcutaneous lump (Fig. 9.3), often with a central punctum (Fig. 9.4) through which its contents may be expressed as a cheese-like material.

Fig. 9.1 Epidermoid cyst. These occur spontaneously and are a smooth dome-shaped mobile swelling.

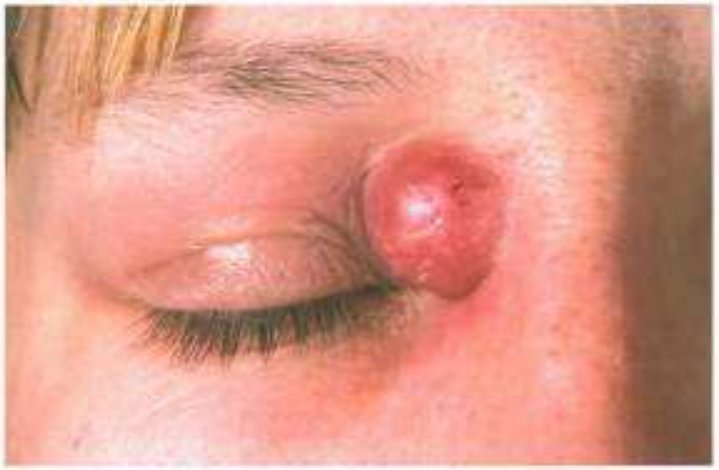


Fig. 9.2 Nodulocystic acne. Epidermoid cysts are common in nodulocystic acne. Their contents may be evacuated via a needle and then injected with triamcinolone.

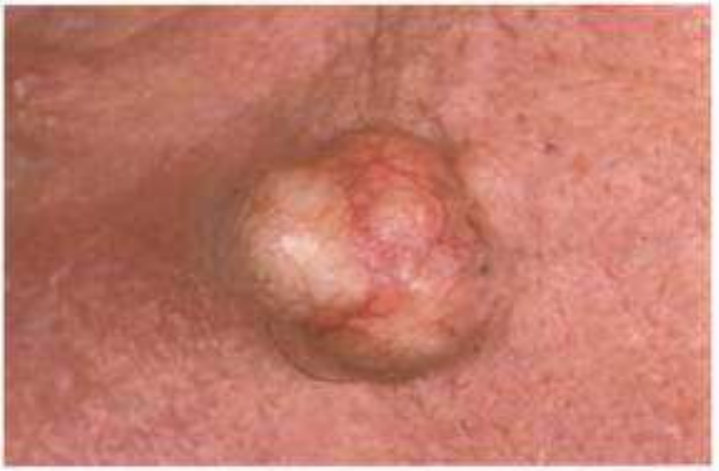


Fig. 9.3 Epidermoid cyst. The cyst is flesh coloured or yellow and is often multilobulated.

Distribution
The face or trunk.

Histopathology
The cyst wall is composed of keratinizing stratified squamous epithelium (Fig. 9.5) and it contains abundant, well-defined keratin lamellae (Fig. 9.6). Rupture of the cyst may result in a foreign body giant cell reaction.

Management
The lesions are harmless but they may be excised. They should be distinguished from:

- developmental **dermoid cysts**. Although these are often present at birth, they may not present until they become infected (Fig. 9.7).

The site (midline scalp or nose) and lateral side of the eye is distinctive, as is the histopathology (Figs 9.8 and 9.9). The wall of the cyst comprises squamous epithelium accompanied by adnexal structures, such as hair follicles and sebaceous glands. It often contains hair shafts.

MILIA (WHITEHEADS)
A small white or cream-coloured epidermoid cyst.

Aetiology
Milia are common in acne. They may complicate any blistering process (Fig. 9.10) that involves the dermo-epidermal junction (e.g. bullous pemphigoid, porphyria cutanea tarda, epidermolysis bullosa or mild sunburn). They are often a feature of chronic solar damage (Fig. 9.11) in association with open comedones (blackheads).

Clinical Features
Symptoms
Milia are asymptomatic.

Morphology
A single or multiple firm, minute white or cream-coloured papules.

Distribution
Milia usually occur on the face (Figs 9.12 and 9.13) but can develop anywhere when related to a blistering process.

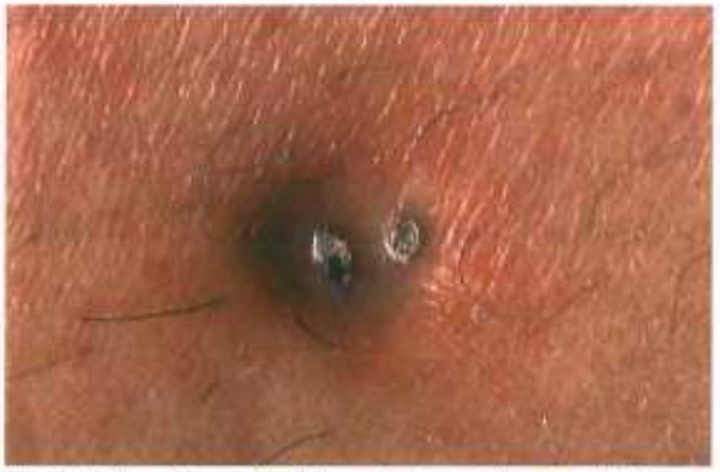


Fig. 9.4 Epidermoid cyst. A central punctum is present through which the contents may be expressed.

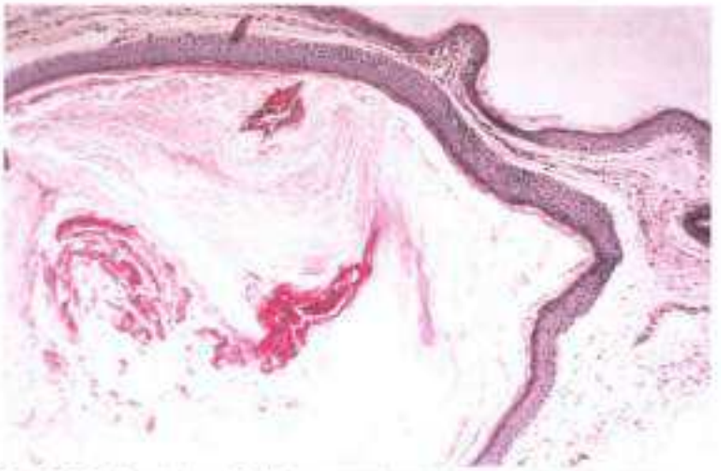


Fig. 9.5 Epidermoid cyst. This low-power view shows part of a discrete cyst located below the surface epithelium.

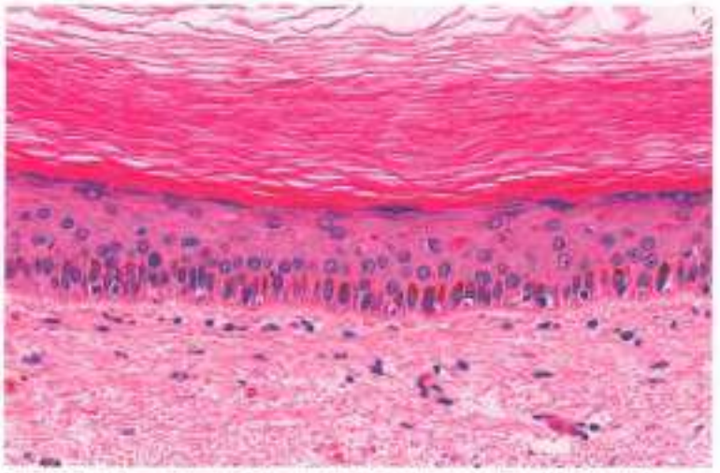


Fig. 9.6 Epidermoid cyst. The cyst wall is composed of keratinizing stratified squamous epithelium with a prominent granular layer. Keratin flakes are present in the cyst lumen. (Courtesy of Dr Jon Salisbury.)

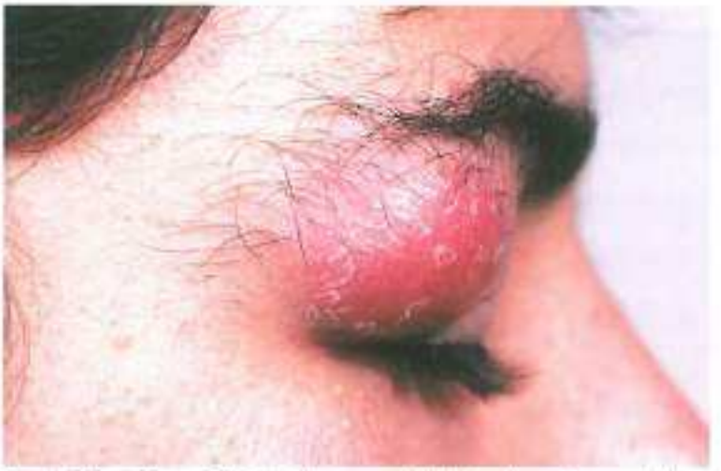


Fig. 9.7 Dermoid cyst. This is a developmental defect and may be present at birth or present later when infected. The lateral side of the eye is a classical site; others are the midline of the scalp, nose or neck.

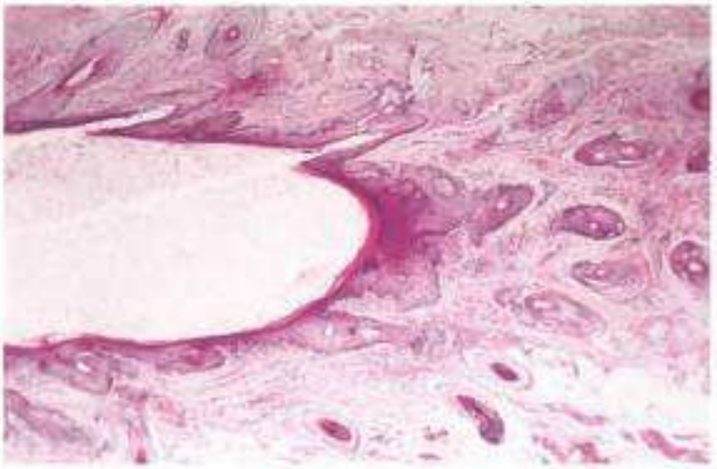


Fig. 9.8 Dermoid cyst. The cyst wall is composed of keratinizing squamous epithelium from which numerous hair follicles and sebaceous glands arise.

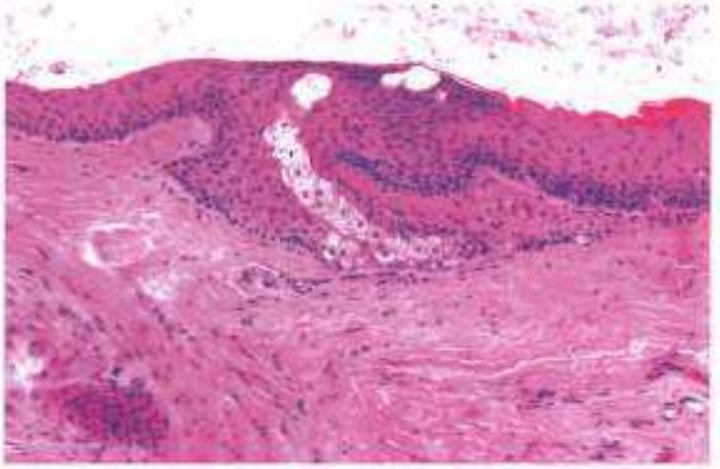


Fig. 9.9 Dermoid cyst. Within the cyst wall, a line of sebaceous glands and also hair follicles are visible. (Courtesy of Dr Jon Salisbury.)

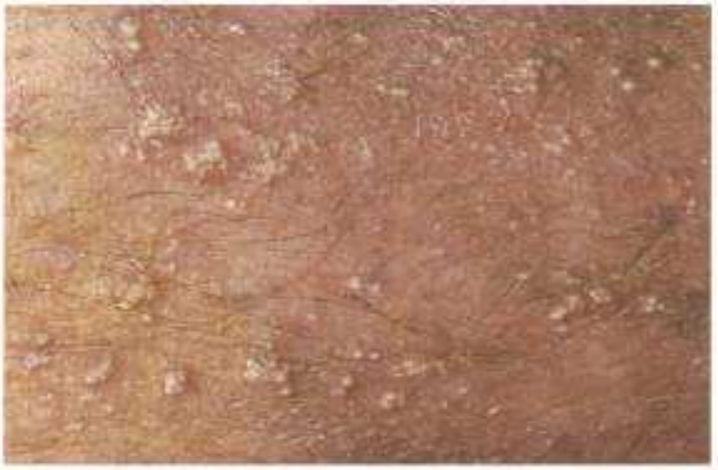


Fig. 9.10 Milia. A myriad of white cysts followed blistering secondary to profound oedema of the legs caused by the nephrotic syndrome.

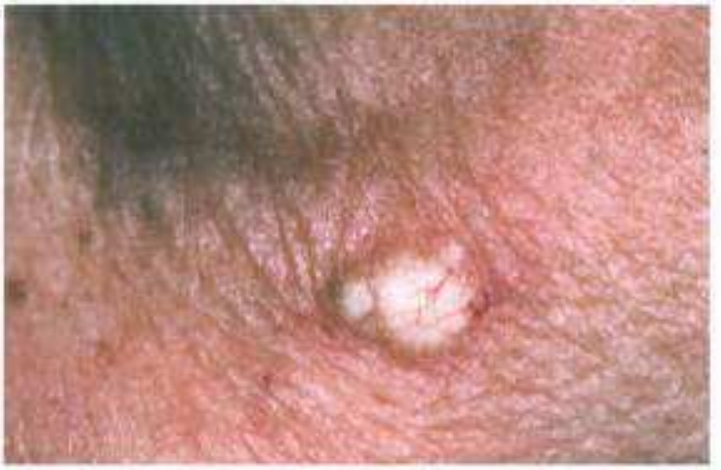


Fig. 9.11 Solar milium. These are common on the face of the elderly, are white (and therefore distinguishable from the yellow of xanthoma) and multilobulated.

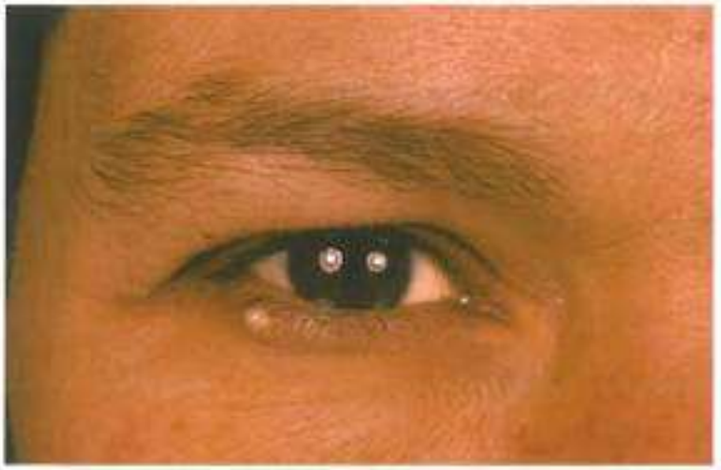


Fig. 9.12 Milium. The lesion is a firm white or cream-coloured papule that occurs most commonly on the face. It is a minute epidermal cyst.

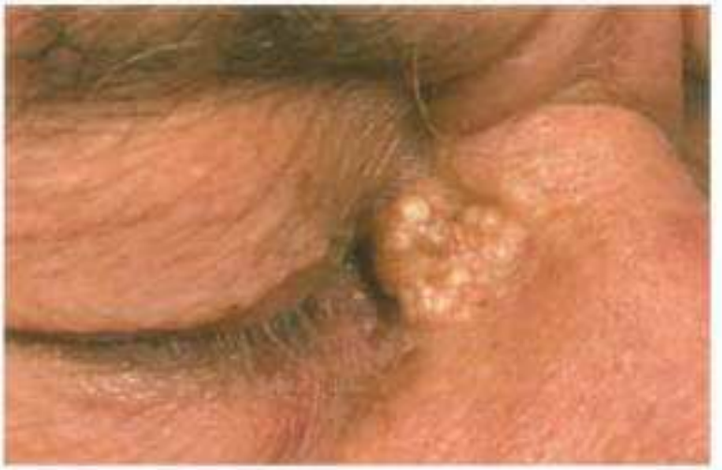


Fig. 9.13 Solar milia. Milia occur as a result of chronic solar damage. They are distinguished from xanthelasma by their white colour.

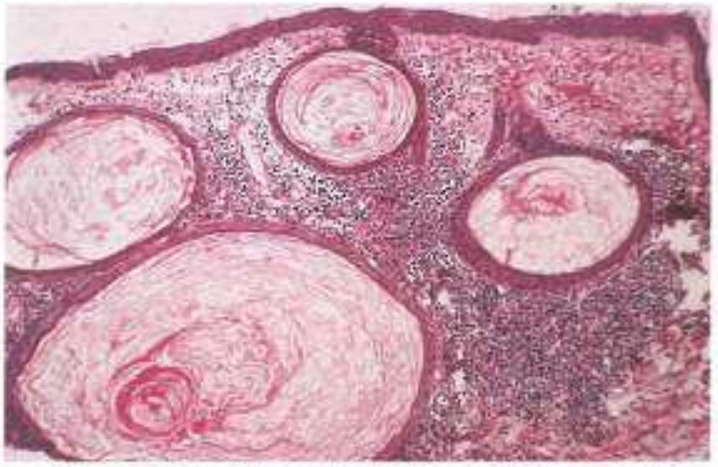


Fig. 9.14 Milia. Four small milia are present in the superficial dermis. Two of them (upper right) are related to eccrine sweat ducts.

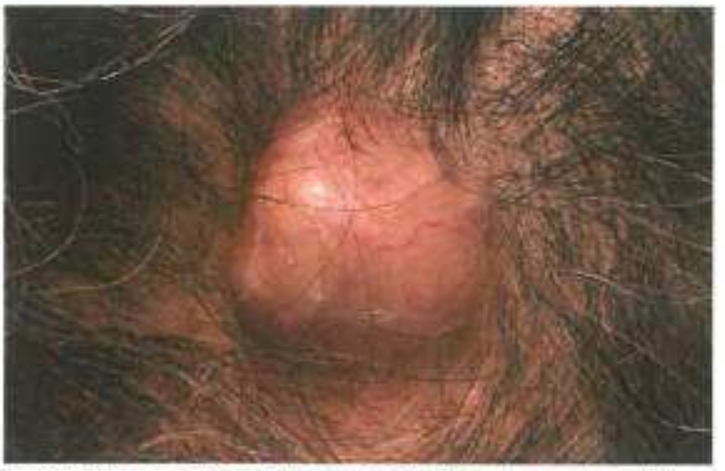


Fig. 9.15 Pilar cyst. The scalp is a common site. The lesions may be multiple and are sometimes hereditary.

Histopathology

A whitehead is a minute epidermoid cyst, situated within the upper dermis. It consists of a thin wall of stratified squamous epithelium surrounding keratin lamellae (Fig. 9.14).

Management

Those associated with acne disappear spontaneously eventually, but they can be easily removed by breaking the skin surface with a sterile needle and scraping out the contents. Larger lesions may be removed through a small incision.

PILAR (TRICHOLEMMAL) CYST

Pilar cysts are derived from the outer root sheath of the hair follicle; they may be multiple on the scalp and inherited as an autosomal dominant, especially in females.

Clinical Features

Symptoms

An asymptomatic lump, especially on the scalp (Fig. 9.15).

Morphology

It is similar to an epidermal cyst except that it does not have a punctum, but it is often difficult to distinguish them except histologically.

Distribution

Commonly on the face and neck. In the scalp, they may be multiple and often are referred to as 'wens' and inherited as an autosomal dominant trait. They are frequently known (erroneously) as sebaceous cysts.

Histopathology

The epithelium of the pilar cyst is derived from the external root sheath of the hair follicle and, therefore, undergoes tricholemmal keratinization (an abrupt transition from epithelium to keratin in the absence of a granular cell layer). The cyst wall is composed of an outer palisaded layer of small basal cells, which merge with larger eosinophilic cells. The latter, in turn, are desquamated, which produces the granular contents of the pilar cyst (Fig. 9.16). Calcification commonly occurs and a foreign body giant cell reaction is sometimes seen following rupture.

Management

The lesion may be excised under local anaesthesia.

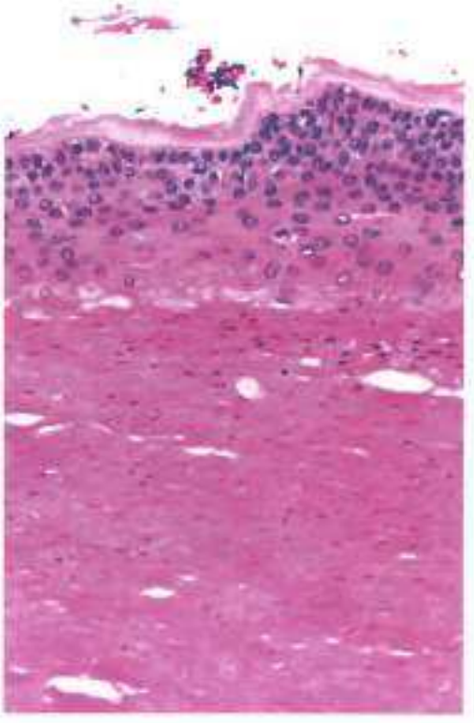


Fig. 9.16 Pilar cyst. These cysts are lined by a stratified squamous epithelium that is undergoing trichilemmal keratinization (sudden keratinization without the formation of a granular cell layer). Focal calcification of the cyst contents is frequent (Courtesy of Dr Jon Salisbury.)

STEATOCYSTOMA MULTIPLEX

An autosomal dominant condition of multiple sebaceous cysts, also known as sebocystomatosis.

Clinical Features

The lesions present at puberty or thereafter.

Morphology

The lesions are multiple, smooth-surfaced flesh- or slightly yellow-coloured cysts 1–3 cm in diameter.

Distribution

The cysts occur most commonly on the neck (Fig. 9.17), over the sternum (Fig. 9.18), on proximal parts of the limbs and axillae (Fig. 9.19).

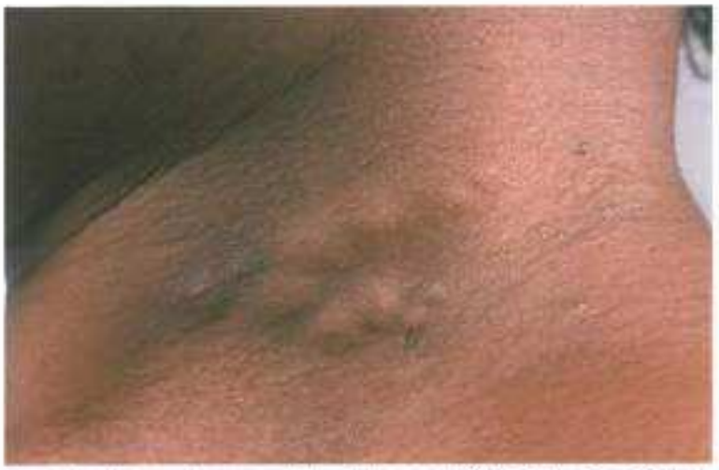


Fig. 9.17 Steatocystomas multiplex. There are multiple slightly yellow-coloured cysts. These are true sebaceous cysts. They present in young adults.

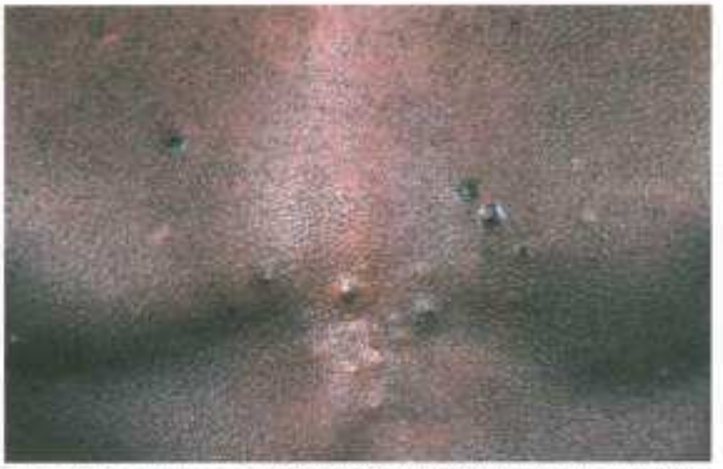


Fig. 9.18 Steatocystoma multiplex. The front of the chest is a common site for these small sebaceous cysts.

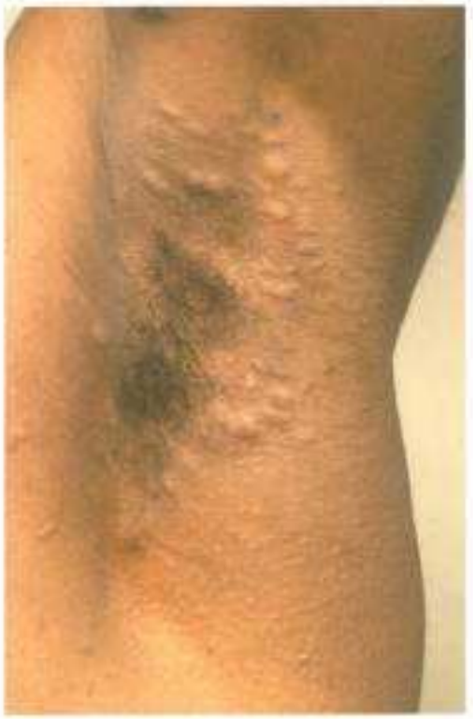


Fig. 9.19 Steatocystoma multiplex. The lesions are multiple and the chest and axillae are common sites. It is usually inherited as an autosomal dominant condition.

Histopathology

It is a variant of a dermoid cyst comprising a thin wall of stratified squamous epithelium from which arise conspicuous sebaceous glands (Fig. 9.20). More rarely, other adnexal structures may be found (e.g. hair follicles and glands).

Management

There are so many cysts that excision is impractical but the tip of an 18 gauge needle may be inserted, the contents aspirated and the sebaceous gland scraped off the wall of the cyst.

ERUPTIVE VELLUS HAIR CYSTS

Vellus hair cysts are lined with squamous epithelium and contain vellus hairs. It may be inherited as an autosomal dominant.

Clinical Features

Symptoms

Numerous small cysts in the skin.

Morphology

The cysts are small, soft, smooth-surfaced, often dome-shaped 1–4 mm cystic papules, which may be flesh coloured (Fig. 9.21), yellow or red.

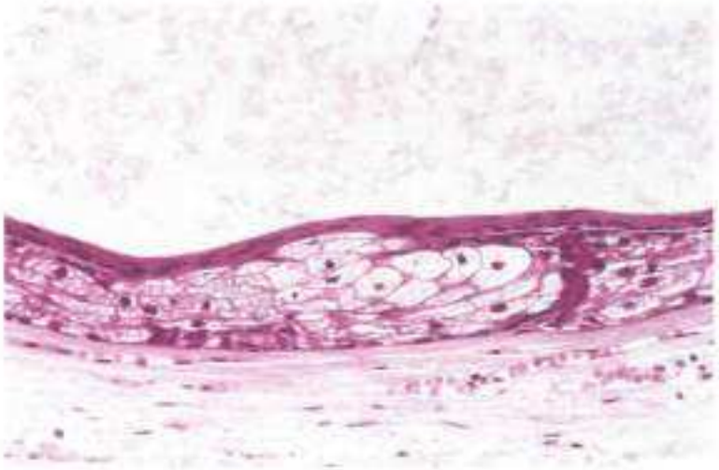


Fig. 9.20 Steatocystoma multiplex. Mature sebaceous cells are present in close apposition to the attenuated squamous epithelium.

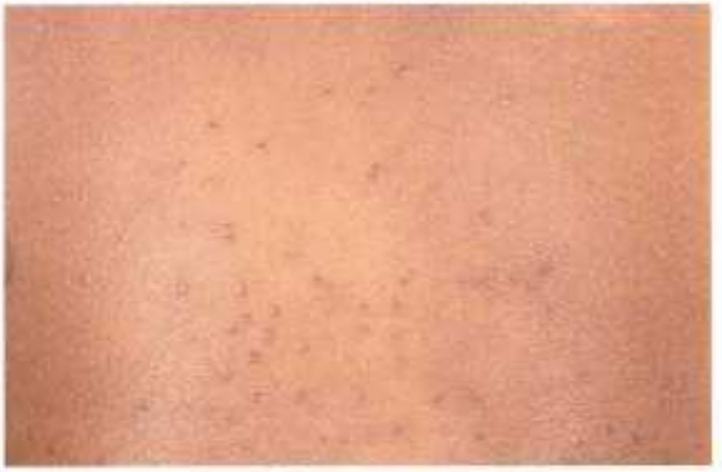


Fig. 9.21 Eruptive hair cysts. The cysts are very small and scattered in profusion across the chest wall.

Distribution
Especially the anterior chest (Fig. 9.22), abdomen and extremities.

Histopathology
The cysts are lined with squamous epithelium containing laminated keratinous material and a variable number of vellus hairs (Fig. 9.23), mostly in the mid dermis with a perivascular lymphocytic infiltrate.

Management
Some resolve spontaneously but many persist. Surgery is usually unsatisfactory. Topical retinoic acid and 12% lactic acid have been reported as helpful, as has laser therapy.

Epidermal tumours

SEBORRHOEIC WART
A common benign abnormality of epidermal basal cell maturation that results in a well-defined, raised, rough-surfaced papule or plaque.

Aetiology
Although common in the elderly, seborrhoeic warts are seen in younger Caucasians who have suffered sunburn in childhood. They result from failure of keratinocyte maturation, which leads to an accumulation of immature yet benign cells within the epidermis. Neighbouring melanocytes may transfer melanin to the abnormal keratinocytes and so the lesions are usually pigmented.

Seborrhoeic warts occur early in adult life as an autosomal dominant condition on the face in black skin and present as pigmented, sometimes pedunculated, papules. This is known as *dermatosis papulosa nigra* (Fig. 9.24).

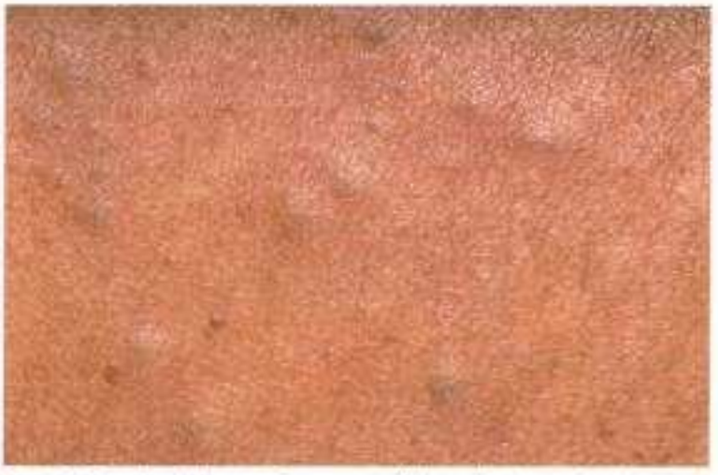


Fig. 9.22 Eruptive hair cysts. There are multiple small cysts seen in close-up. Vellus hairs are found in the cyst wall.

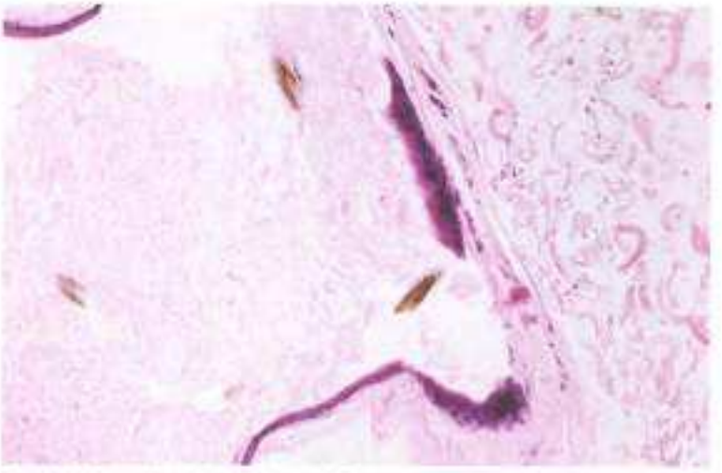


Fig. 9.23 Eruptive vellus hair cysts. The cysts are lined with squamous epithelium containing laminated keratinous material and vellus hairs.

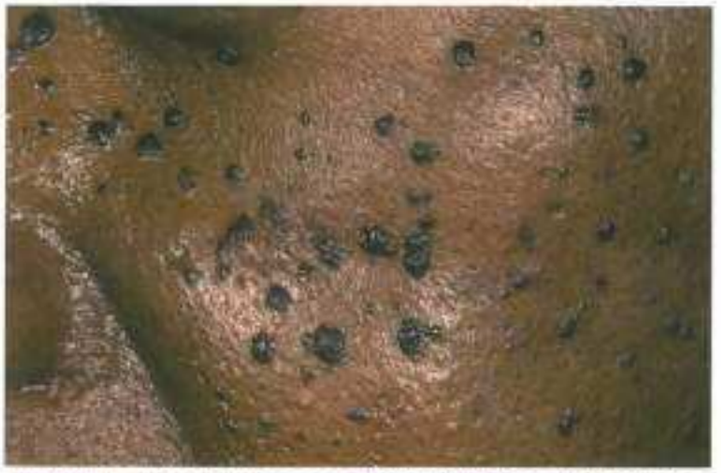


Fig. 9.24 Dermatosis papulosa nigra. There are multiple pigmented papules on the face. They occur in black skins and are inherited as an autosomal dominant.

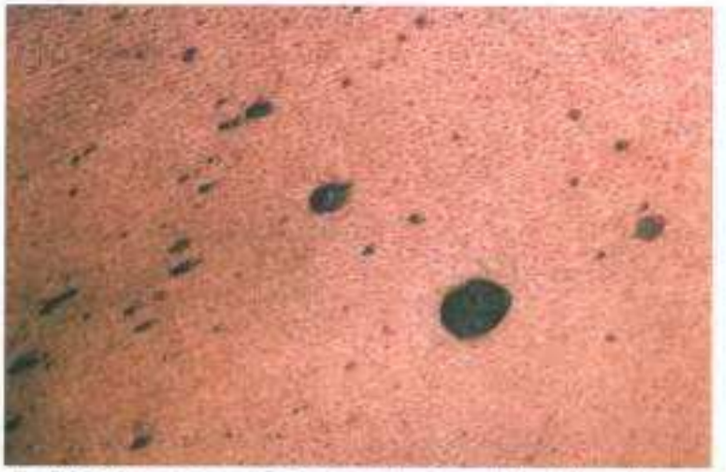


Fig. 9.25 Seborrhoeic warts. They vary in size from quite tiny to larger lesions. A rhynid is present here. They can occur in Middle Eastern and Asian skin types.

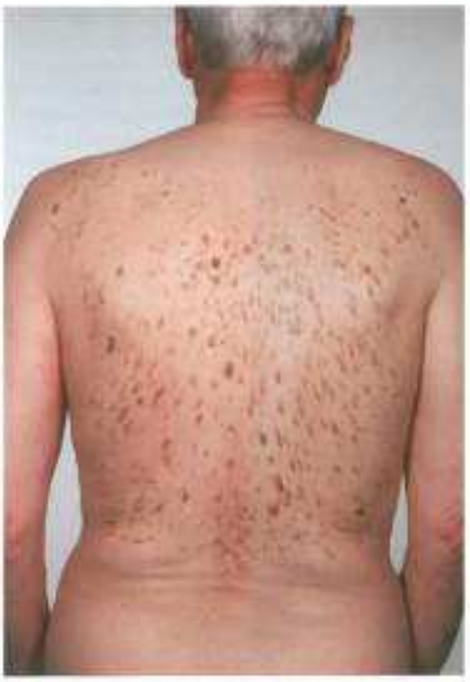


Fig. 9.26 Seborrhoeic warts. Lesions may occur in profusion and vary in depth of pigmentation and size. Note the sparing of the buttocks, which suggests that they are solar related.

Clinical Features

Symptoms

Usually asymptomatic but sometimes itch or become inflamed.

Morphology

Seborrhoeic warts have a variety of appearances, which may cause confusion. Lesions may be big or small (Fig. 9.25) and may occur singly or in large numbers (Fig. 9.26). The essential features are that the wart has a well-defined border with a rough surface, which may be fissured or stippled in appearance. The colour of each lesion is uniform, but varies, depending on the amount of melanin taken up by the immature keratinocytes. It may range from yellow (Fig. 9.27) to tan, brown or black. The seborrhoeic wart is usually raised and often appears to have been stuck onto the skin (Fig. 9.28); conversely, it may be hardly raised at all. They may become irritated and inflamed (Fig. 9.29). Sometimes, the lesions may be pedunculated, especially around the eyes or in the flexures. Small pale rough-surfaced well-defined papules on the lower legs and ankles are known as *stucco keratoses* (Fig. 9.30).

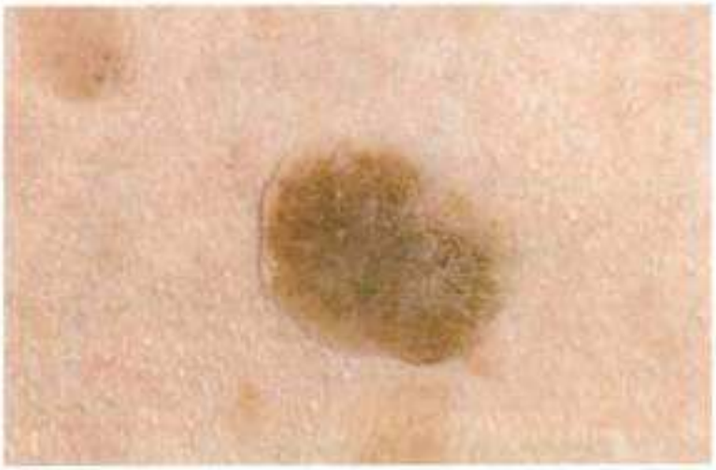


Fig. 9.27 Seborrhoeic wart. The lesion has a rough and finely fissured surface; it is well defined and often has a yellow-brown greasy appearance (hence seborrhoeic).

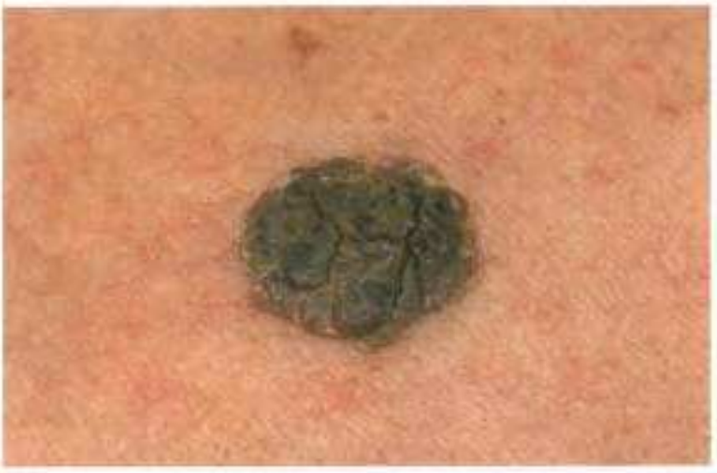


Fig. 9.28 Seborrhoeic wart. This lesion is dark brown with a fissured and stippled surface, which is highly characteristic, and permits distinction from a malignant melanoma.

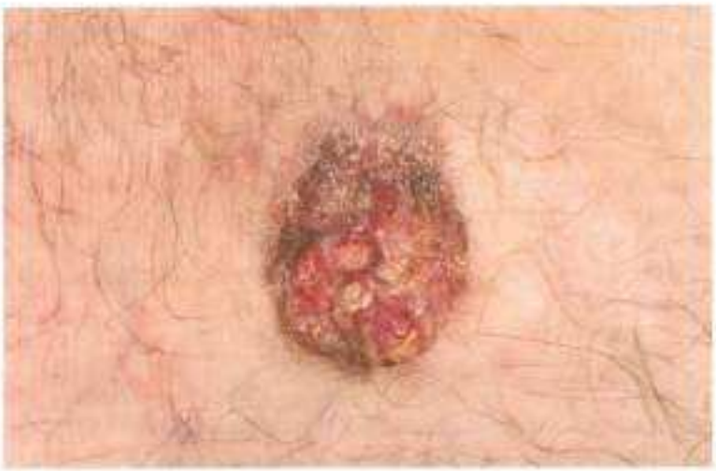


Fig. 9.29 Irritated seborrhoeic wart. The lesion is inflamed and has bled but it is well defined and has a fissured surface.

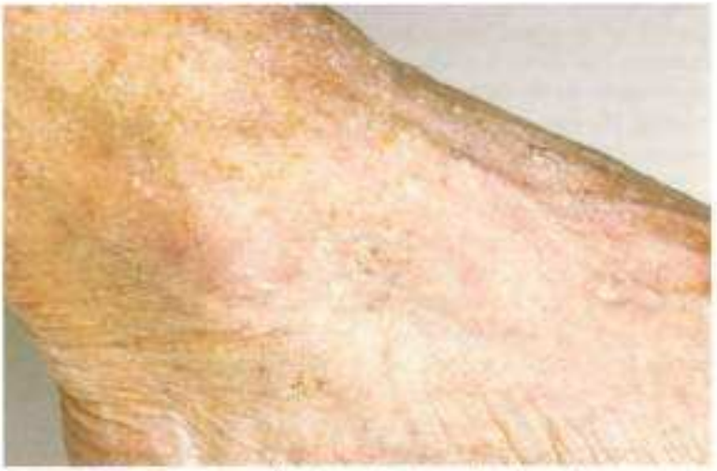


Fig. 9.30 Stucco keratoses. Multiple small pale roughened papules occur on the ankles and lower legs. They are secondary to solar damage.

Fig. 9.31 Seborrhoeic warts. They may occur under breasts in females. This may be caused by sunburn and damage to the chest in childhood, although the lesions arise much later on.

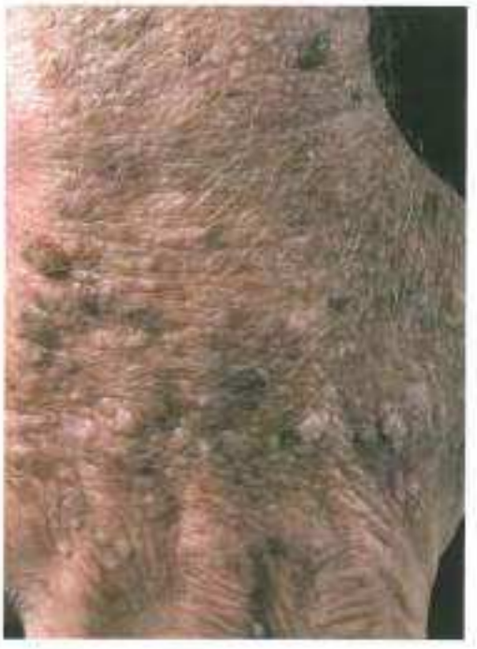


Fig. 9.32 The signs of Leser Trelat. The rapid onset of a myriad of seborrhoeic warts may be associated with malignant disease. This man had acanthosis nigricans and an adenocarcinoma of the stomach.

Fig. 9.33 Seborrhoeic keratosis (hyperkeratotic type). There is papillomatosis and hyperkeratosis of an acanthotic epidermis composed principally of cytologically bland, basal cells. The keratinocytes are deficient in high molecular weight keratins. (Courtesy of Dr Jon Salisbury.)

Fig. 9.34 Pigmented seborrhoeic keratosis (acanthotic type). This seborrhoeic keratosis shows acanthosis and pseudohorn cysts. Many of the epidermal cells contain melanin pigment, as a result of transfer from neighbouring melanocytes. (Courtesy of Dr Jon Salisbury.)

Distribution

Usually on areas that have at some stage been exposed to the sun and, therefore, rare on the buttocks. They are frequently multiple, but may be found under the breasts (Fig. 9.31) secondary to prepubertial exposure and burning. The explosive onset of many seborrhoeic warts may be associated with malignancy (Fig. 9.32).

Histopathology

Seborrhoeic warts are composed of an admixture of small basal cells and keratinocytes and display a variety of patterns. The keratotic (papillomatous) type is most common. It is characterized by hyperkeratosis, acanthosis, papillomatosis and horn cyst formation (Fig. 9.33). The acanthotic variant typically has a smooth surface and is often heavily pigmented (Fig. 9.34). The adenoid type is less common. It is characterized by a downgrowth of thin proliferating epidermal strands. The irritated seborrhoeic wart (inverted follicular keratosis) is characterized by the development of conspicuous squamous whorls or 'eddies' (Fig. 9.35). Stucco keratoses show dense orthokeratosis and 'peaked' acanthosis (Fig. 9.36).

Management

It is the most common differential diagnosis of a malignant melanoma, but is quite harmless. It may, however, be removed surgically under local anaesthesia by either curettage or shaving it off flush to the skin with a scalpel blade. This leaves behind characteristic tiny pinpoint bleeding, which should be gently cauterized to avoid unnecessary scarring. Pedunculated lesions may be removed with scissors. Liquid nitrogen is a simple non-invasive technique that is particularly effective for smaller lesions. Its advantage is that many seborrhoeic warts can be frozen rapidly; the disadvantage is that histopathological examination is not possible.

A condition with an identical histology to stucco keratoses is *acrokeratosis verruciformis of Hopf*. However, the latter is usually present at birth or in early childhood and affects not only the dorsa of the feet but also of the hands, elbows, knees and flexures; in addition, there are rather distinctive small keratoses on the palms and there is a risk of transformation to squamous cell carcinoma. The nails may be brittle, ridged, hyperkeratotic and discoloured. There is a P602L missense mutation in the ATP2A2

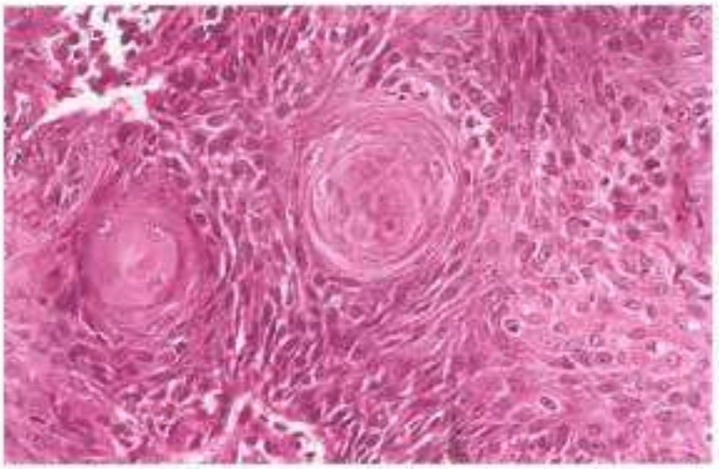


Fig. 9.35 Irritated seborrhoeic wart. 'Differentiation' with the formation of whorls of squamous cells within the epidermis (so-called 'squamous eddies') is typical.

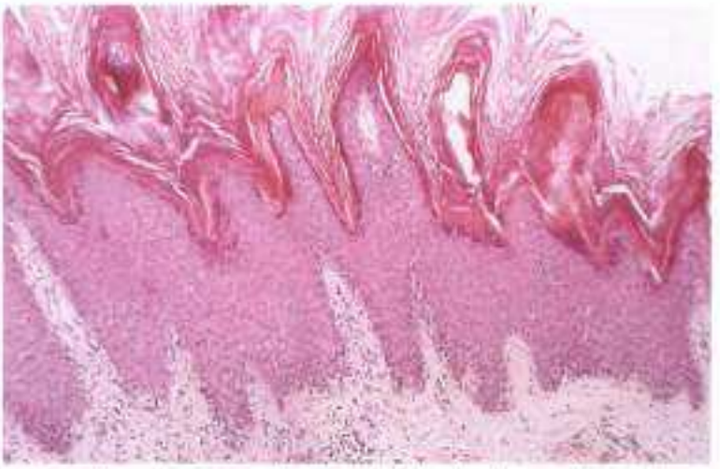


Fig. 9.36 Stucco keratoses. There is marked hyperkeratosis and acanthosis forming multiple peaks like church spires.

gene which encodes SERCA2, which is responsible for transport of Ca^{2+} from the cytoplasm to sarcoplastic and endoplastic reticulin, resulting in dysregulation of epidermal differentiation and cellular adhesion.

ACANTHOMA FISSURATUM

A pseudoepithelial tumour induced by the chronic trauma of heavy spectacle frames (spectacle frame granuloma).

Clinical Features

Symptoms

An uncomfortable lesion on top of or behind the ear or on the bridge of the nose.

Morphology

A thickened plaque with a noticeable linear groove (Fig. 9.37).

Distribution

The position of the lesion relates to the weight of the spectacles.

Histopathology

This is non-specific, with hyperkeratosis, acanthosis and dermal chronic inflammation with fibrosis.

Management

Replacement of the heavy frame by a lighter model usually resolves the problem. Occasionally excision is necessary.

CLEAR CELL ACANTHOMA OF DEGOS

An epidermal lesion containing clear cells with a glycogen-rich cytoplasm.

Clinical Features

Symptoms

It may bleed.

Morphology

The lesion is a small, well-defined, slightly elevated, red nodule with tiny red puncta on its surface (Fig. 9.38). It has a thin scale that is adherent peripherally and leaves a moist or bleeding surface when removed.

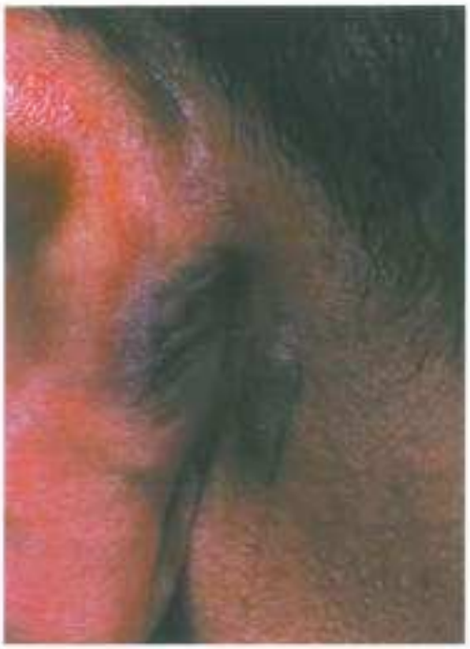


Fig. 9.37 Acanthoma fissuratum. A linear groove indents the thickened plaque caused by heavy spectacle frames behind the ears.

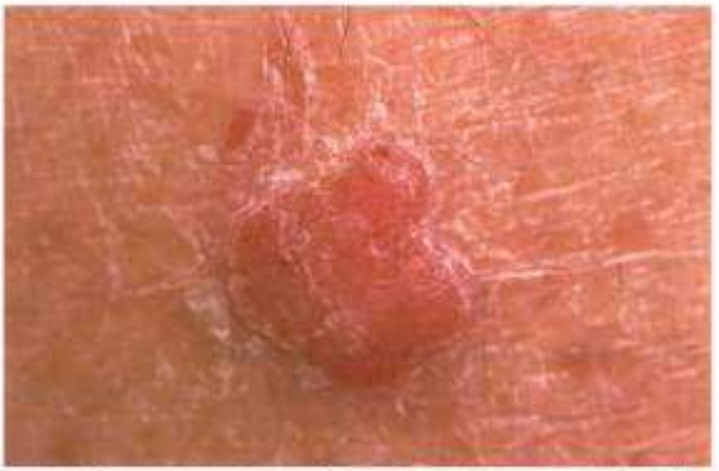


Fig. 9.38 Clear cell acanthoma of Degos. The nodule is red, well defined with tiny red puncta on its surface. Note the thin adherent peripheral scale. It is benign. (Courtesy of the Institute of Dermatology.)

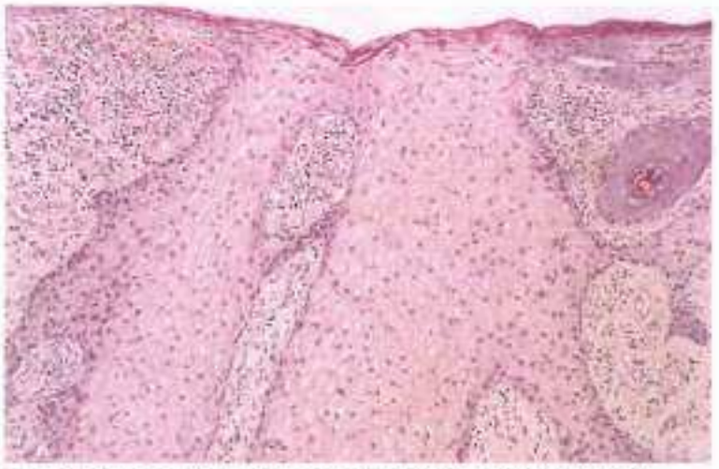


Fig. 9.39 Clear cell acanthoma of Degos. The epidermis shows marked acanthosis. Note the extreme pallor of the keratinocytes. Adnexal epithelium is uninvolved. It is an uncommon lesion.

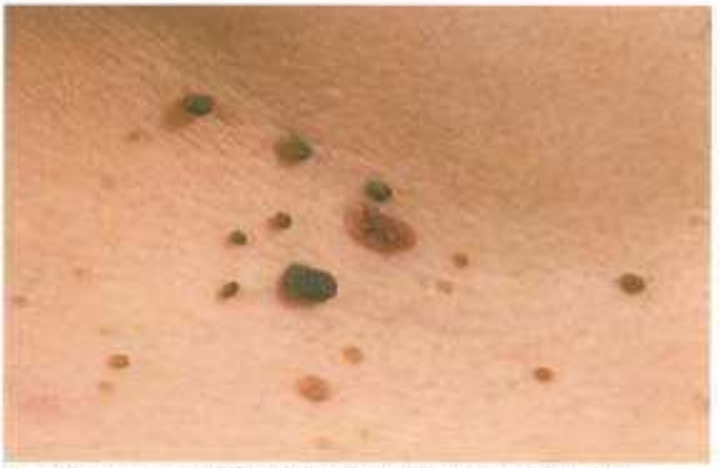


Fig. 9.40 Skin tags. These are either tiny raised lesions or pedunculated pigmented soft papules that often occur in profusion around the neck. Seborrhoeic warts are also present.

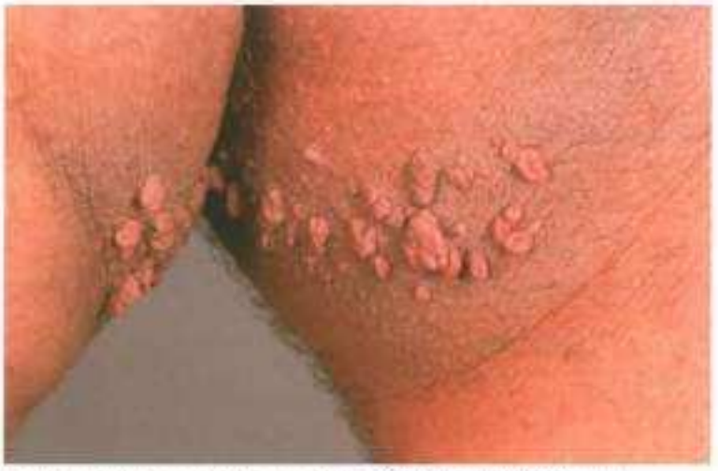


Fig. 9.41 Pseudoacanthosis nigricans. Skin tags are usually present in association with pigmentation and velvety thickening of the skin (pseudoacanthosis nigricans), obesity and insulin resistance.

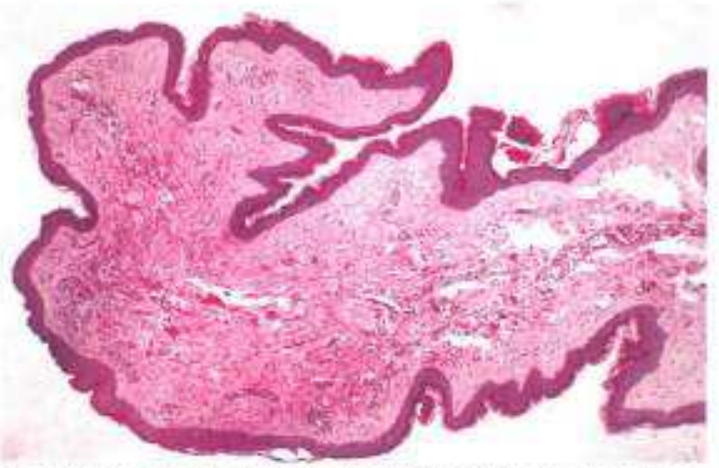


Fig. 9.42 Fibroepithelial polyp. The polyp is composed of mature keratinizing squamous epithelium overlying a fibrovascular core.

Distribution
The lower leg is the common site. Multiple lesions may occur.

Histopathology
The tumour has a well demarcated lateral border. It is papillomatous and acanthotic. The tumour cells are pale (Fig. 9.39) as a result of abundant intracytoplasmic glycogen, which may be demonstrated by the periodic acid–Schiff (PAS) reaction.

Management
The lesion may be curetted or excised for pathological examination.

SKIN TAGS (FIBROEPITHELIAL POLYPS)
Common, small, soft, pigmented papules, which are often pedunculated and may be multiple; they occur around the neck and in the flexures.

Aetiology
Skin tags (acrochordons) occur in both sexes and increase in incidence with advancing years. They often grow during pregnancy and fall off afterwards. They occur in profusion with obesity, pseudoacanthosis nigricans and insulin resistance. A quarter of these patients have non-insulin-dependent diabetes mellitus. Skin tags also occur in malignant acanthosis nigricans.

Clinical Features
Symptoms
Minor protrusions which are often cosmetically unacceptable.

Morphology
A flesh-coloured or pigmented papule which may be minute or pedunculated.

Distribution of skin tags
It may be solitary, particularly in the groin or axillae, or be present in profusion, particularly around the neck (Fig. 9.40) and in the flexures in the obese (Fig. 9.41).

Histopathology
There is mature keratinizing squamous epithelium, which overlies a fibrovascular core (Fig. 9.42). Sometimes clinically identical lesions turn out histologically to be seborrhoeic warts or pedunculated melanocytic naevi.

Management
Small lesions can be cauterized without anaesthesia. The discomfort is momentary and no worse than the prick of a local anaesthetic. More pedunculated lesions can be removed with scissors with or without local anaesthesia or with a cutting cautery.

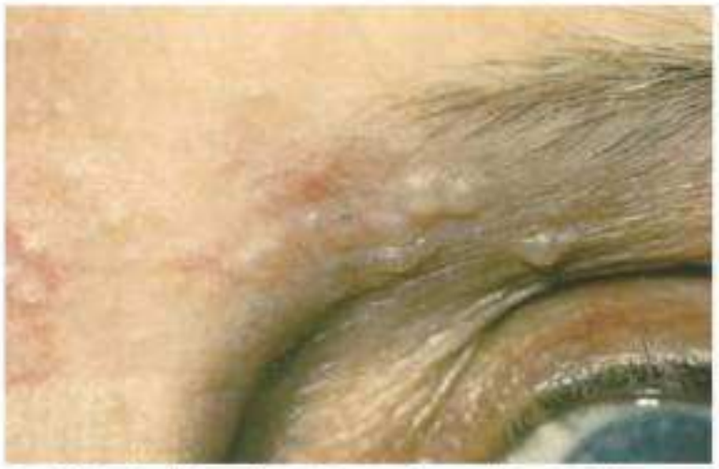


Fig. 9.43 Eccrine hydrocystoma. There are tense vesicles particularly periorbitally. They increase in size in hot conditions and may virtually disappear in winter. (Courtesy of the late Dr Neil Smith.)

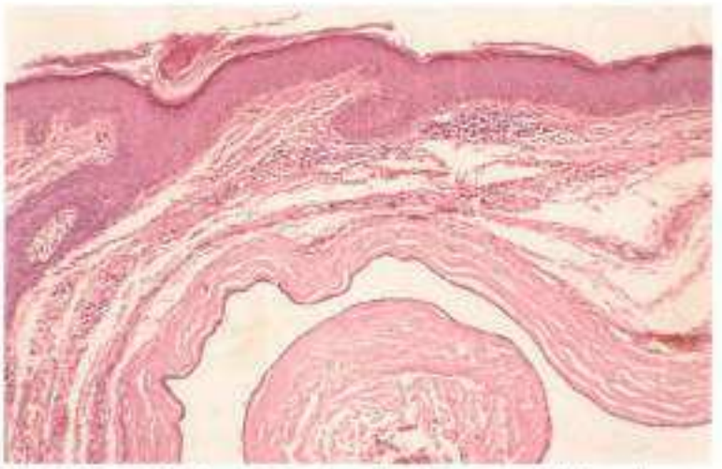


Fig. 9.44 Eccrine hydrocystoma. The cyst wall is composed of fibrous tissue lined by cuboidal epithelial cells.

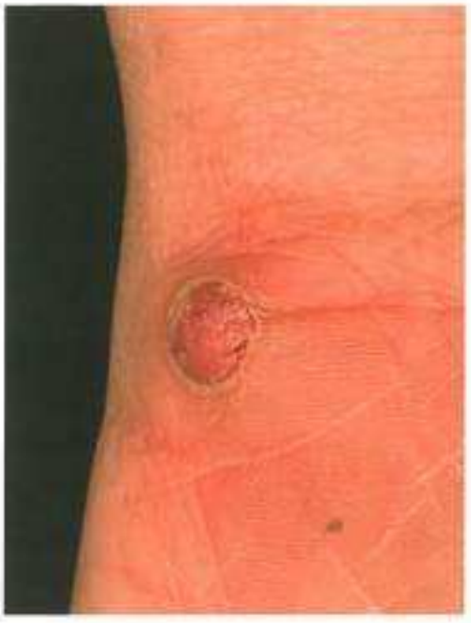


Fig. 9.45 Eccrine poroma. The palm of the hand is a common site. Note that the lesion is surrounded by a thickened collar of epidermis.

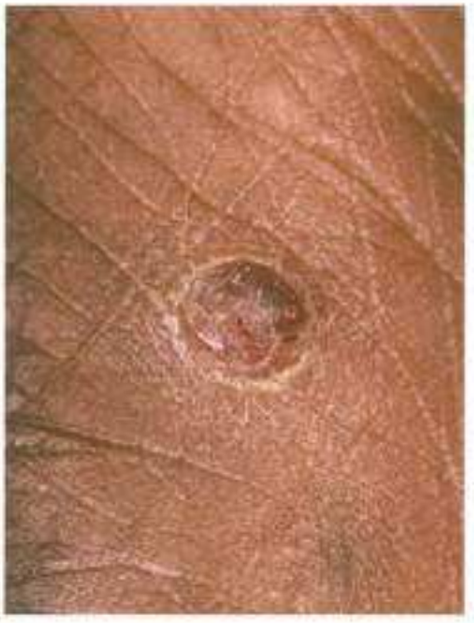


Fig. 9.46 Eccrine poroma. The pink nodule is surrounded by a thin moat with a hyperkeratotic border on the sole of this West Indian's foot.

Sweat gland tumours

ECCRINE HIDROCYSTOMA

A rare disorder of the eccrine sweat duct that results in several small swellings, usually adjacent to the eyelid.

Clinical Features

Symptoms

Multiple small swellings that increase in size with heat and become almost imperceptible in the winter.

Morphology

Tense vesiculopapular lesions (Fig. 9.43).

Distribution

Mainly around the eyes.

Histopathology

The cyst is lined by a double layer of cuboidal epithelial cells with an eosinophilic cytoplasm (Fig. 9.44).

Management

Their variation in size reflects the ambient temperature. They are most common in females and cooks. Air conditioning may be helpful.

ECCRINE POROMA

A nodule arising from the intraepidermal component of the eccrine sweat duct.

Clinical Features

Symptoms

An asymptomatic lump, usually on the palm or sole.

Morphology

A solitary pink or red plaque or nodule (Fig. 9.45) with a characteristic thickened rim of epidermis, which looks like a moat (Fig. 9.46).

Distribution

The favoured site is the palm or sole.

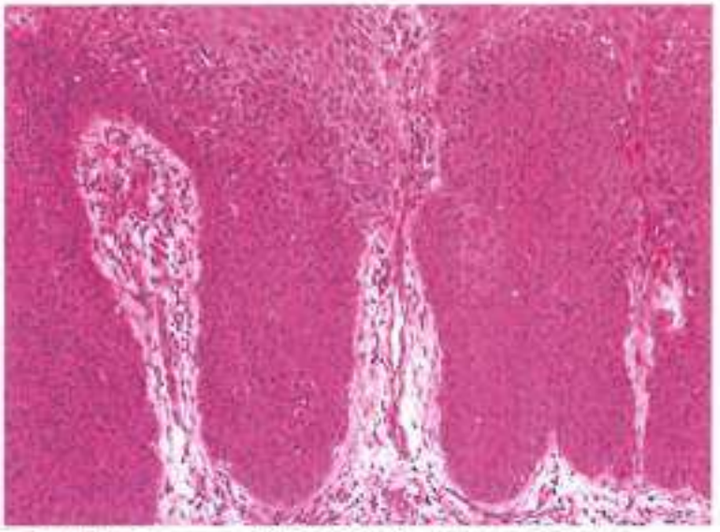


Fig. 9.47 Eccrine poroma. This is a highly cellular tumour replacing the epidermis and growing as broad anastomosing bands into the dermis. (Courtesy of Dr Jon Salisbury.)

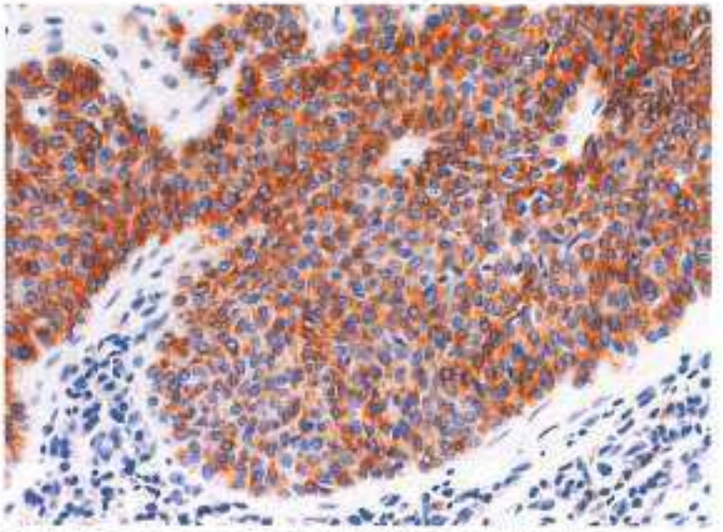


Fig. 9.48 Eccrine poroma. The tumour cells stain positively for epithelial membrane antigen (EMA). (Courtesy of Dr Jon Salisbury.)

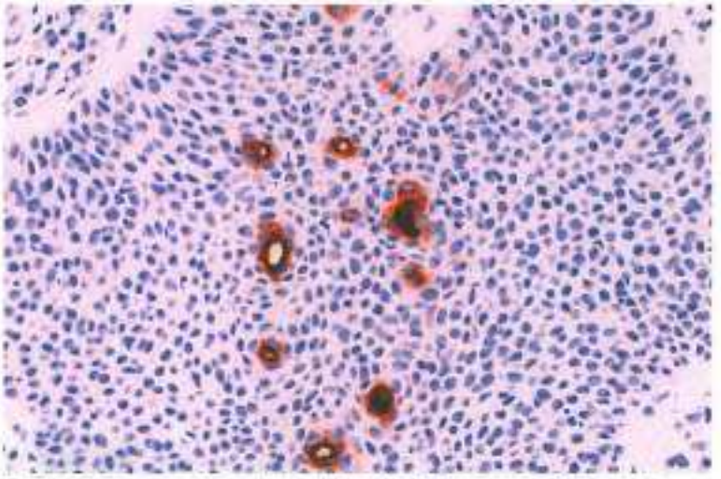


Fig. 9.49 Eccrine poroma. Immunohistochemical staining for CEA (carcino-embryonic antigen) highlights the duct structures. (Courtesy of Dr Jon Salisbury.)

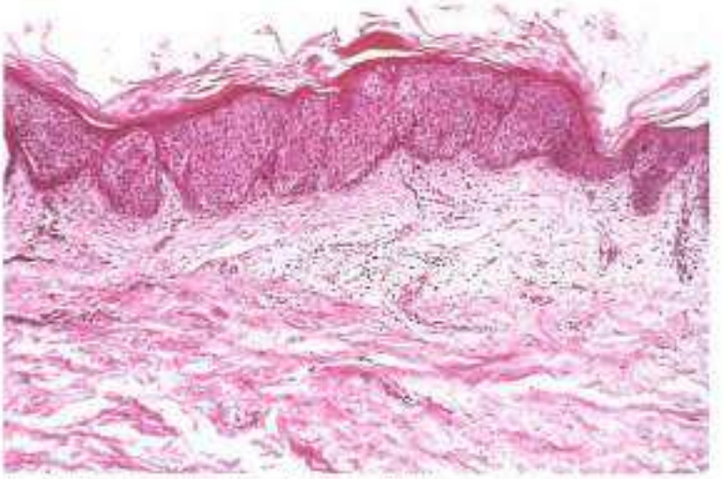


Fig. 9.50 Borst–Jadassohn epithelioma. This phenomenon refers to circumscribed nests of neoplastic cells occurring amongst normal keratinocytes and may occur in eccrine poroma or a seborrhoeic wart.

Histopathology

The tumour replaces the epidermis and grows into the dermis as broad anastomosing bands (Fig. 9.47). The tumour cells stain positively for epithelial membrane antigen (Fig. 9.48) and regularly form duct-like structures (Fig. 9.49). There is a sharp demarcation between the keratinocytes and the monomorphic smaller cuboidal tumour cells. This histopathological appearance of a nest of neoplastic cells among normal keratinocytes was formerly known as *Borst–Jadassohn epithelioma* (Fig. 9.50). Similar intraepithelial nesting patterns may occur in seborrhoeic warts, hidroacanthoma simplex and Bowen's disease.

Management

A close relative is a *nodular hidradenoma* (Fig. 9.51). It is however a dermal tumour and occurs on the limbs and body but not on the palm or sole. Eccrine poromas should be excised as they may become malignant.

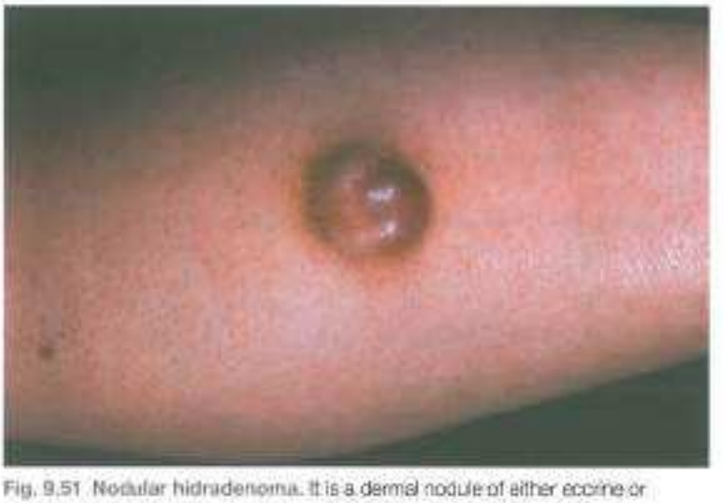


Fig. 9.51 Nodular hidradenoma. It is a dermal nodule of either eccrine or apocrine derivation. It may contain a minimal quantity of fluid but is usually diagnosed pathologically.

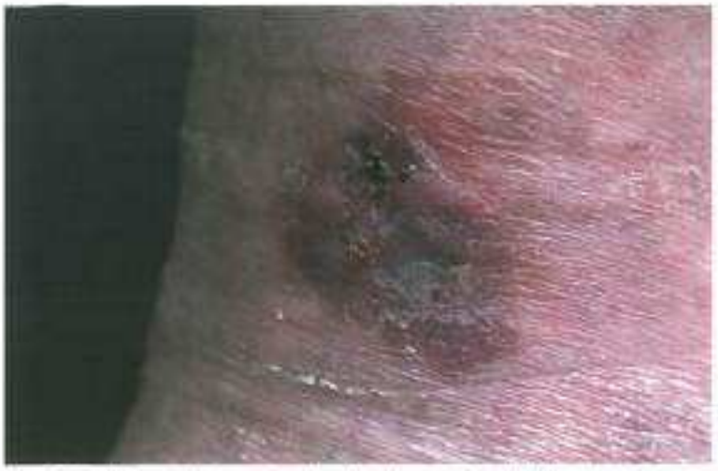


Fig. 9.52 Hidroacanthoma simplex. There is a raised well-defined erythematous plaque that looks like Bowen's disease. A biopsy established the diagnosis. (Courtesy of Dr H. Woolfson.)

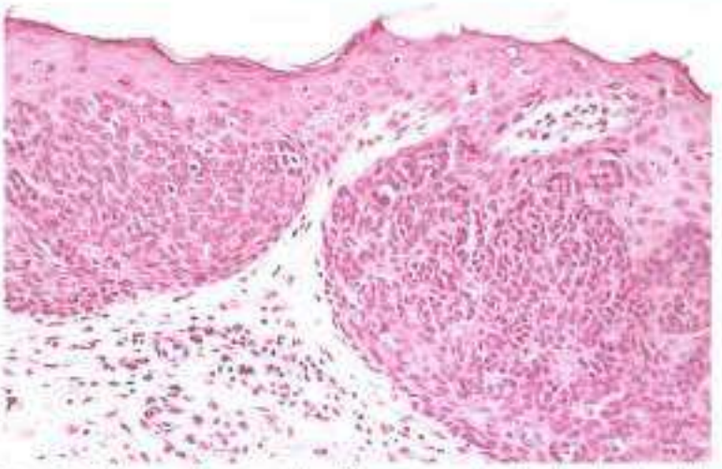


Fig. 9.53 Hidroacanthoma simplex. There are several nests of uniform basaloid cells within the epidermis, which are distinct from the surrounding keratinocytes (the Borst–Jadassohn phenomenon).

HIDROACANTHOMA SIMPLEX

A rare tumour of acrosyringal differentiation which may be an intraepidermal variant of eccrine poroma (intraepidermal acrospiroma).

Clinical Features

An asymptomatic plaque in older age groups.

Morphology

A flat or slightly raised, irregular, verrucose brown plaque simulating Bowen's disease or a seborrhoeic wart (Fig. 9.52).

Distribution

Usually found on the lower extremity or trunk.

Histopathology

There are nests of small uniform basaloid cells with small nuclei that are distinct from the surrounding keratinocytes (Fig. 9.53) (the Borst–Jadassohn phenomenon). The enzymatic staining activity is the same as eccrine sweat glands.

Management

The diagnosis is rarely made prior to excision and pathological examination.

SYRINGOMA

A benign, usually multiple tumour of sweat ducts.

Aetiology

Syringomas are common in Orientals and Afro-Caribbeans. They are occasionally inherited as an autosomal dominant genetic abnormality of 16q22. They occur in Down's syndrome.

Clinical Features

Symptoms

Asymptomatic blemishes occurring on the skin, particularly around the eyes.

Morphology

Small, smooth-surfaced, flesh-coloured papules.

Distribution

Symmetrically, particularly around the eyes in females (Fig. 9.54 and 9.55) but also on the face, in the axillae, on the chest or genitalia and on

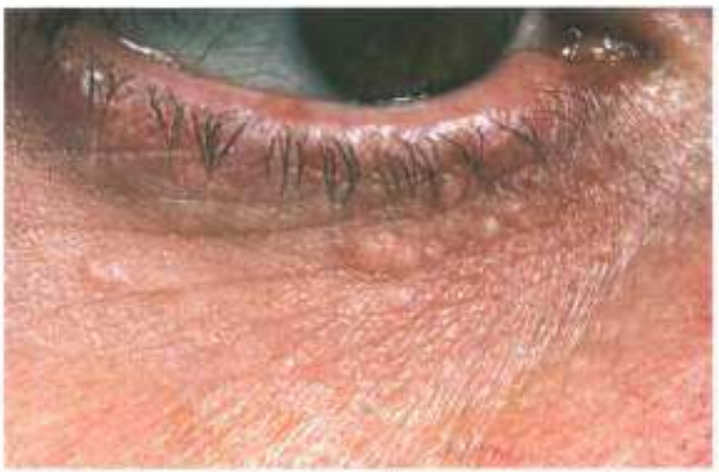


Fig. 9.54 Syringomas. The lesions are small, smooth-surfaced, often flesh-coloured papules, particularly located around the eyes.

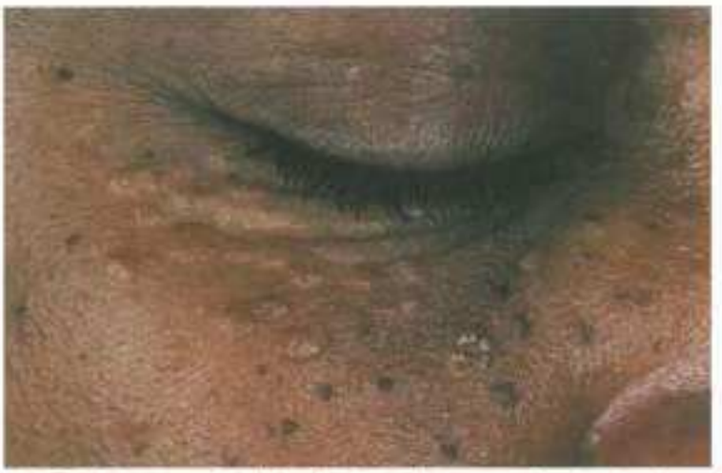


Fig. 9.55 Syringomas. The lesions directly under the eye are flesh-coloured papules and are syringomas. These contrast well with the dark warty papules which are dermatosis papulosa nigra.

the neck (Fig. 9.56). They may be very extensive (Fig. 9.57) and can sometimes arise in an eruptive manner (*hidradenome eruptif*, Fig. 9.58).

Histopathology

There are within the dermis small, irregular, cleft-like glandular spaces (Fig. 9.59). The spaces are usually lined by a double layer of epithelium, and tangential cutting gives rise to a tadpole-like appearance (Fig. 9.60). There is some dispute as to whether it is of apocrine or eccrine differentiation in origin.

Management

Syringomas are harmless and may be ignored or ablated with gentle cautery.

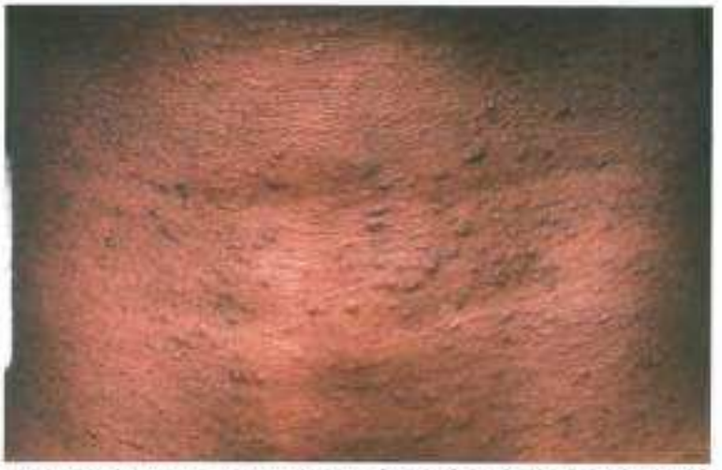


Fig. 9.56 Syringomas. The front of the neck is a common site. There are multiple small pigmented papules.

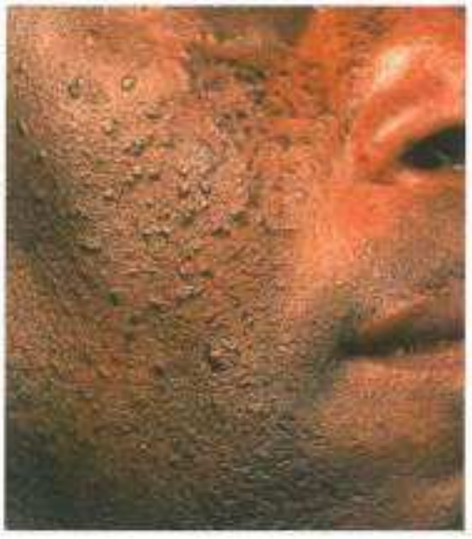


Fig. 9.57 Syringomas. The lesions may be extensive and pigmented in black skin. A biopsy is often required to establish the diagnosis.

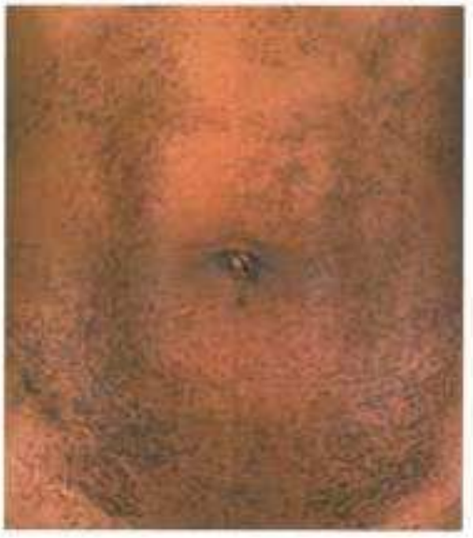


Fig. 9.58 Syringomas. Occasionally the pigmented papules of syringomas erupt in profusion (hidradenome eruptif).

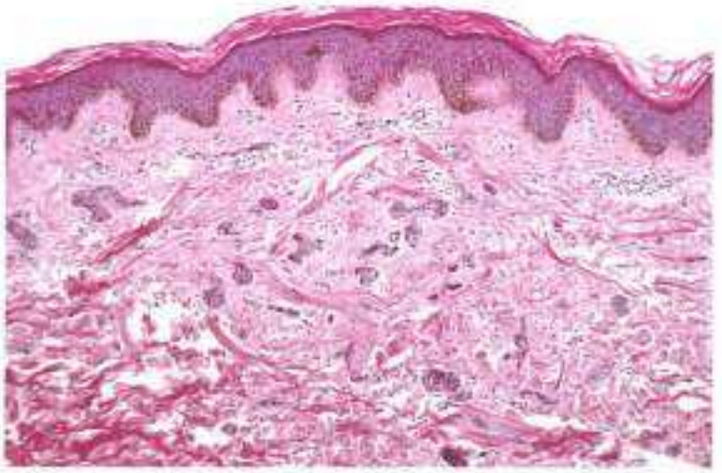


Fig. 9.59 Syringoma. A small number of glandular spaces occupy the mid-dermis.

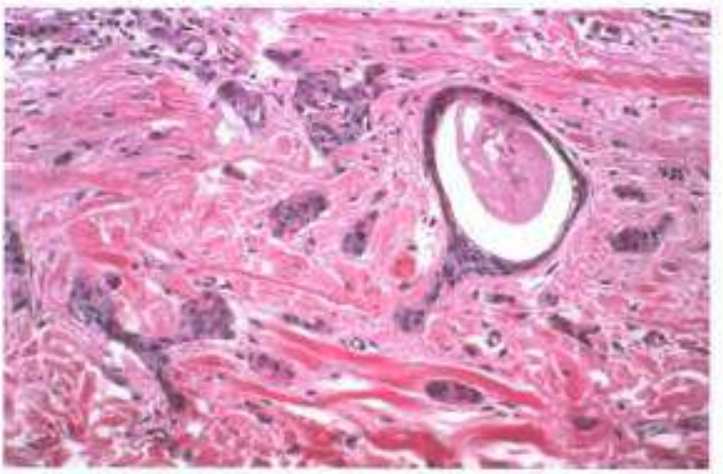


Fig. 9.60 Syringoma. In the right side of the field is a 'tadpole' gland – so typical of syringomas. Elsewhere the epithelial islands are not canalized.

SPIRADENOMA

A solitary tender bluish nodule, the origin of which is in dispute. It may be eccrine or apocrine.

Clinical Features

It appears as a tender, painful lump.

Morphology

There is a firm, tender, round, bluish dermal nodule (Fig. 9.61).

Distribution

Usually solitary on the trunk or proximal limbs, but multiple lesions in a zosteriform nevoid distribution have been described.

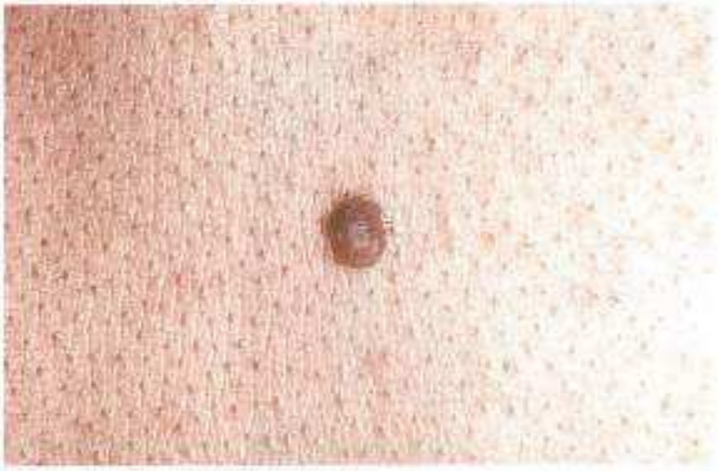


Fig. 9.61 Spiradenoma. There is a small slightly bluish nodule that is characteristically painful. (Courtesy of Dr Philip McKee.)

Histopathology

It is closely related to a dermal cylindroma and may occur together as part of *Brooke–Spiegler syndrome*. There are lobules of two cell types (Fig. 9.62). One is larger and paler and they are grouped around small tubular structures or cystic spaces. The other is smaller and darker and distributed at the periphery. The lobules are surrounded by condensed connective tissue.

Management

It is painful, and this with its blue colour may suggest the diagnosis. Excision is the treatment of choice.

CHONDROID SYRINGOMA

Also known as *mixed tumour of the skin*, it is a nodule that is probably of eccrine origin most commonly found in males in middle age.

Clinical Features

Symptoms

An asymptomatic lump.

Morphology

A flesh-coloured nodule.

Distribution

Usually on the face (Fig. 9.63), trunk or extremities.

Histopathology

It is a fairly large multilobulated tumour that is similar to an eccrine spiroadenoma but with other areas more apocrine in character. The epithelial cells have an eosinophilic cytoplasm and an oval basophilic nucleus and there are ducts lined with an inner layer of rather flat cuboidal cells and an outer layer of myoepithelial cells set in a mucopolysaccharide and pseudocartilaginous stroma.

Management

Chondroid syringoma may be excised.

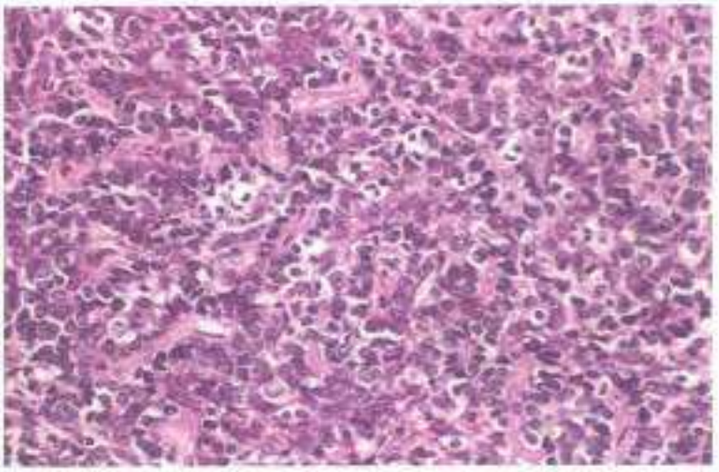


Fig. 9.62 Spiradenoma. There are two cell populations. The outer layer have small hyperchromatic nuclei. The inner are larger with round or oval vesicular nuclei. (Courtesy of Dr Philip McKee.)

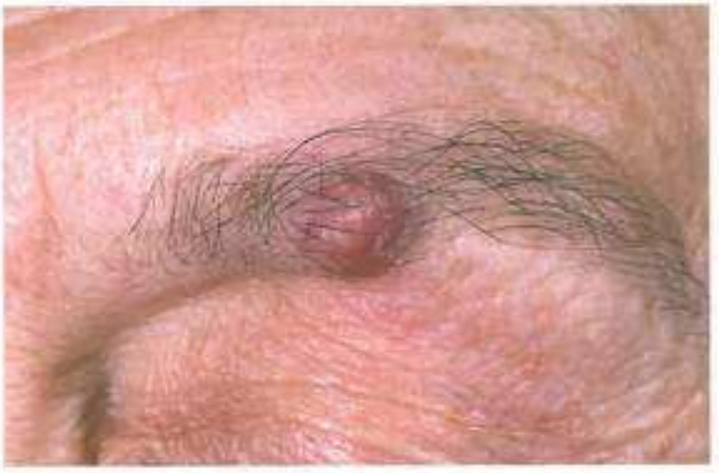


Fig. 9.63 Chondroid syringoma. There is a flesh-coloured nodule. It is rarely diagnosed prior to excision.

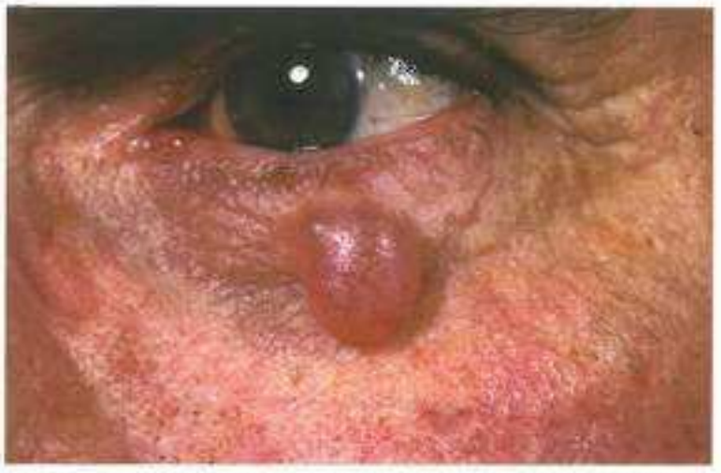


Fig. 9.64 Apocrine hidrocystoma. There is a dome-shaped nodule just below the eye, which is a characteristic site.

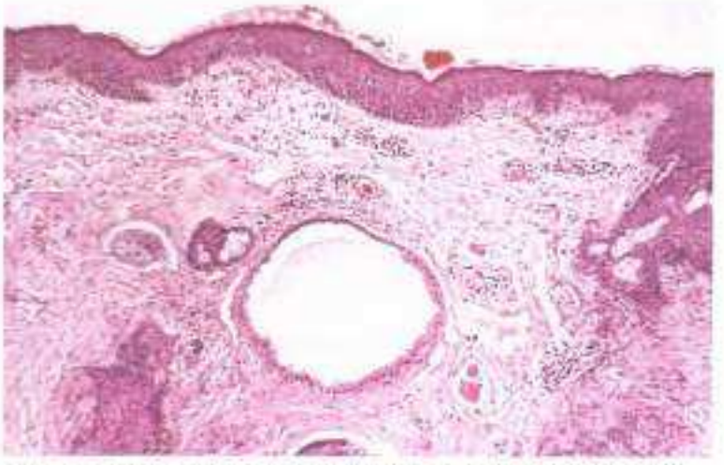


Fig. 9.65 Apocrine hidrocystoma. In this early example, the cyst wall can be seen, lined with tall eosinophilic cells that show so-called 'decapitation' secretion.

Apocrine gland tumours

APOCRINE HIDROCYSTOMA (CYSTADENOMA)

A benign cystic tumour of the apocrine secretory glands.

Clinical Features

Symptoms

A slow-growing lump on the face in middle age.

Morphology

The lesion is a solitary dome-shaped, large bluish swelling (Fig. 9.64). Unlike its eccrine variant it shows no seasonal variation.

Distribution

Apocrine hidrocystoma occurs on the face, particularly around the eye.

Histopathology

Apocrine hidrocystoma consists of one or more intradermal cystic spaces (Fig. 9.65), lined by a double layer of epithelium. The outer flattened cells are of myoepithelial derivation. The inner layer consists of tall columnar cells with eosinophilic cytoplasm and basally located round or oval vesicular nuclei, which often show decapitation secretion.

Management

The lesion may be excised. Occasionally multiple lesions occur which may respond to 1450 nm diode laser.

Hair follicle tumours

These may be single or multiple. The latter are usually genetically determined and include the CYLD cutaneous syndromes, Cowden's syndrome, Birt–Hogg–Dubé and generalized basaloid follicular hamartoma.

DERMAL CYLINDROMA

A common benign large tumour of hair follicle origin, arising from stem cells in the bulge region of the hair follicle.

Aetiology

Although usually a solitary tumour in adults, particularly females, many lesions may occur on the scalp in association with multiple trichoepithelioma. Sometimes there may be so many that the entire scalp is covered (Fig. 9.66) and it is known as the *turban tumour*. It is inherited as an autosomal dominant condition. There is loss of the cylindromatosis tumour suppressor gene (CYLD) on chromosome 16. Heterozygous mutations in the CYLD gene locus have been identified as the cause of familial cylindromatosis, Brooke–Spiegler syndrome and multiple familial trichoepitheliomas, conditions characterized by a predisposition to inherited skin appendageal tumours, the diagnostic hallmark of which is the cylindrome. They should probably be renamed CYLD cutaneous syndromes.

Fig. 9.66 Turban tumour. Multiple disfiguring lesions are present. This is often inherited as an autosomal dominant condition. (Courtesy of Queen Victoria Hospital, East Grinstead.)

Clinical Features

Symptoms

A slow-growing, occasionally painful tumour on the head or neck.

Morphology

A smooth-surfaced nodule with noticeable telangiectasia (Fig. 9.67); it can vary in size but it is usually greater than 1 cm in diameter.

Distribution
The head, particularly the scalp and neck.

Histopathology
It is distinctive and is composed of multiple tumour lobules surrounded by an intensely eosinophilic hyaline mantle (Fig. 9.68). Within the lobules are two cell types. Situated predominantly peripherally are palisaded small cells with oval, dark nuclei and negligible cytoplasm. Within the lobules are larger cells with prominent vesicular nuclei; in places, these cells are associated with hyaline material similar to the mantle. Intralobular duct formation may be conspicuous.

Management
The lesions should be excised before they become too large. They are often clinically confused with basal cell carcinomas.

TRICHOFOLLICULOMA
A hamartoma of the pilosebaceous follicle, resulting in the formation of immature and mature hair structures, which protrude from its surface.

Clinical Features
Symptoms
Trichofolliculoma appears as an asymptomatic lump on the face or neck.

Morphology
There is a dome-shaped, flesh-coloured or reddish nodule with a central pore from which delicate hairs protrude (Fig. 9.69).

Distribution
Trichofolliculomas are most common on the face (Fig. 9.70) or neck.

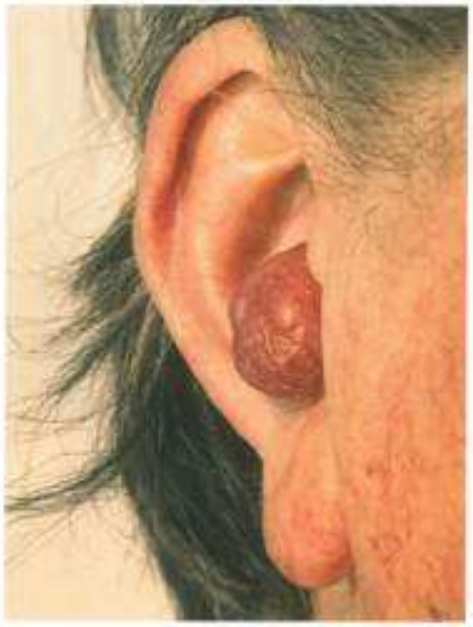


Fig. 9.67 Cylindroma. The lesion is a substantial red nodule. The head and neck are most commonly involved.

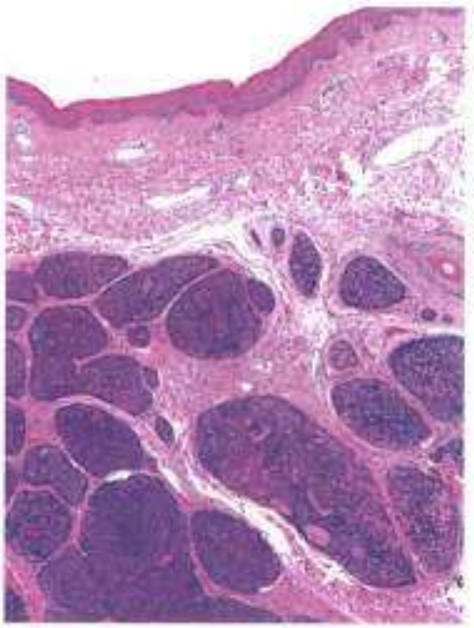


Fig. 9.68 Cylindroma. Well-demarcated 'cylinder'-like cords of small, basophilic tumour cells are present within the dermis, separate from the epidermis. Thick eosinophilic material surrounds, and is present within, the tumour islands. (Courtesy of Dr Jon Salisbury.)

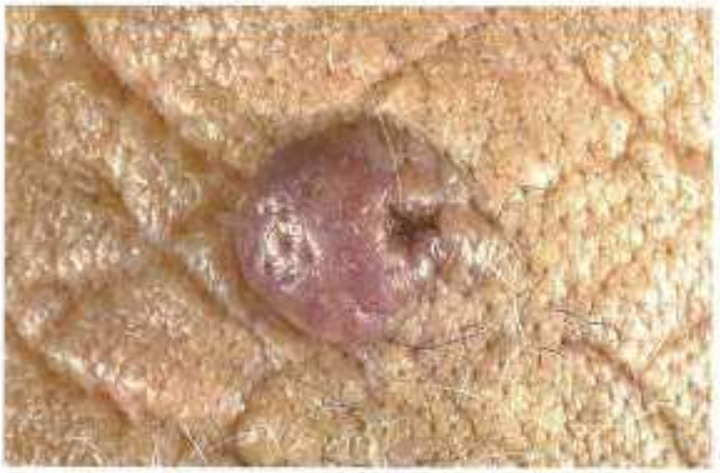


Fig. 9.69 Trichofolliculoma. A dome-shaped nodule is present with a central pore from which hair protrudes. The face or neck are common sites.

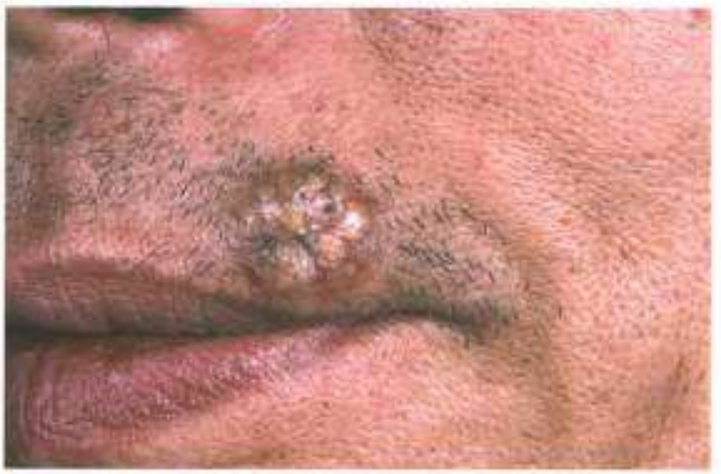


Fig. 9.70 Trichofolliculoma. There is a red nodule with a central depression through which hair may protrude.

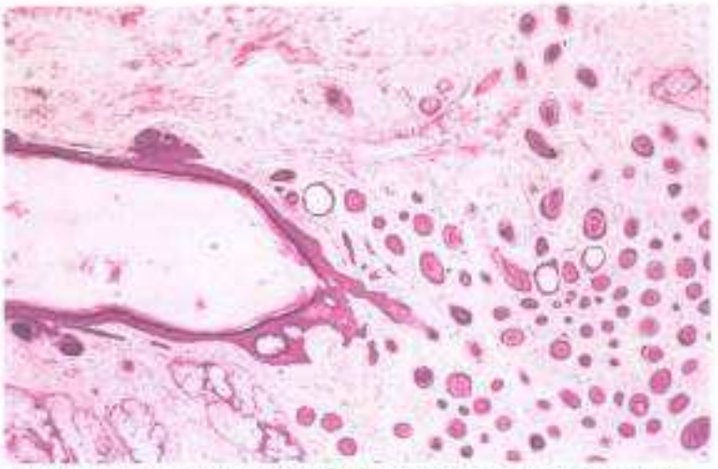


Fig. 9.71 Trichofolliculoma. In this low-power view, numerous small hair germ structures can be seen adjacent to and arising from a cystically dilated pre-existent follicle.

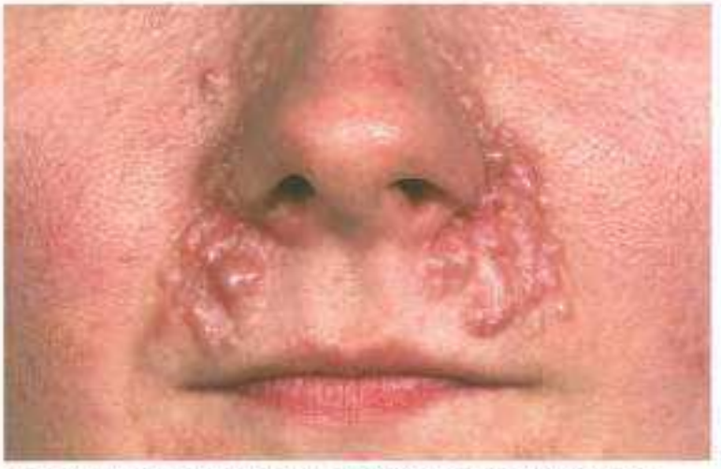


Fig. 9.72 Multiple trichoepithelioma. Multiple skin-coloured papules and nodules are present around the nasolabial folds. They also occur on the eyelids.

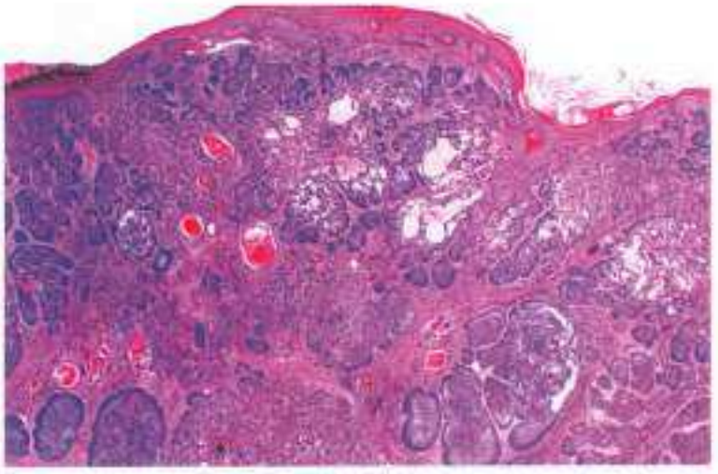


Fig. 9.73 Trichoepithelioma. These hair follicle tumours show stromal elements surrounding islands of basaloid cells with abortive pilar differentiation. The main histological differential diagnosis is with basal cell carcinoma. (Courtesy of Dr Jon Salisbury)

Fig. 9.74 Trichoepithelioma. Solitary lesions do occur but it is not usually diagnosed until it is excised and examined pathologically.

Histopathology

The trichofolliculoma, which may or may not communicate with the surface epidermis, consists of a cystic cavity lined by keratinizing stratified squamous epithelium from which numerous primordial hair follicles arise (Fig. 9.71). Many of these are well developed and contain a central hair shaft, which can be particularly clearly visualized under polarized light. The follicles are surrounded by concentric lamellae of fibrous tissue (perifollicular connective tissue sheaths).

Management

It occasionally becomes malignant and, therefore, should be excised.

MULTIPLE TRICHOEPITHELIOMA

An autosomal dominantly inherited disfiguring condition of multiple tumours of hair follicle origin, particularly affecting the face.

Aetiology

Multiple trichoepithelioma (*epithelioma adenoides cysticum of Brooke*) is linked to a region on chromosome 9p21 that encodes for a number of tumour suppressor genes. The lesions appear after puberty and gradually increase in number and size. It is often associated with cylindromas.

Clinical Features

A disfiguring condition particularly affecting the face.

Morphology

Multiple skin-coloured or pink papules and nodules, often with a telangiectatic surface.

Distribution

The face, including the ears, cheeks, eyelids and nasolabial folds (Fig. 9.72), and sometimes on the neck and upper trunk.

Histopathology

It is similar to a keratotic basal cell carcinoma and composed of islands of small basophilic cells that show peripheral palisading and central, conspicuous keratin cyst formation (Fig. 9.73). Occasionally, abortive hair forms are present.

Management

Management is unsatisfactory. Partial destruction is followed by recurrence and there are usually too many lesions for formal surgical excision. Solitary lesions do occur (Fig. 9.74) and these are usually diagnosed as basal cell carcinomas prior to their excision.

TRICHILEMMOMA

A solitary tumour of the outer root sheath of the hair follicle on the face or neck of the elderly. Multiple lesions occur in *Cowden's syndrome*.

Aetiology

A single lesion may be of no significance but the diagnosis of trichilemmoma may be suggestive of Cowden's syndrome, a rare autosomal dominant condition characterized by multiple hamartomas affecting various organs derived from all three germinative layers associated with increased risk of thyroid, pancreatic and breast cancer and polyposis coli which is usually evident in early adult life. There are also facial trichilemmomas, oral papillomatosis (giving rise to a cobblestone appearance in the mouth, tongue [Fig. 9.75] and gums [Fig 9.76]), acral keratoses, lipomas and angiomas. There are germline mutations in the *PTEN* (*MMAC1*) tumour suppressor gene, at locus 10q22-23. Other PTEN hamartoma tumour syndromes include *Bannayan–Riley–Ruvalcaba* syndrome, an autosomal dominant condition with a variable phenotype including macrocephaly, developmental delay, pseudopapilloedema, hamartomatous growths (subcutaneous and visceral lipomas), gastro-intestinal polyposis, capillary and combined vascular malformations, café-au-lait macules and pigmented macules of the glans penis.

Clinical Features

Symptoms

Asymptomatic lesions on the face.

Morphology

Each lesion is a small warty or smooth flesh-coloured papule (Fig. 9.77).

Distribution

The face, particularly around the nose.

Histopathology

The trichilemmoma is a proliferation of the outer root sheath. It consists of a lobule, or lobules, that arises from the epidermis (Fig. 9.78), composed of small uniform cells with round or vesicular nuclei that show

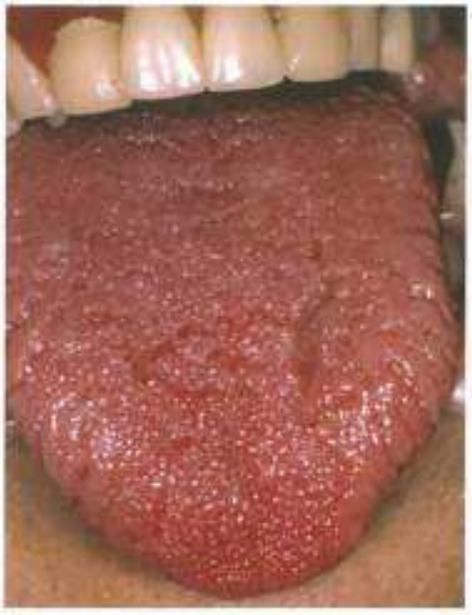


Fig. 9.75 Cowden's syndrome. Oral papillomatosis is characteristic of this dominant condition of multiple facial trichilemmomas, lipomas and palmar pits associated with thyroid, breast or pancreatic cancer. Similar white papillomas occur on the gingiva. (Courtesy of Drs Nigel Burrows and Alvin Chong.)

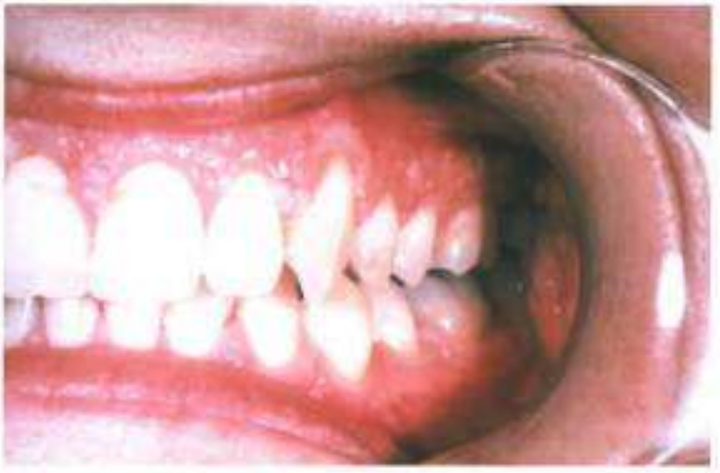


Fig. 9.76 Cowden's syndrome. Multiple flesh-coloured small (1–3 mm) papules are present on the gums. (Courtesy of Drs Nigel Burrows and Alvin Chong.)

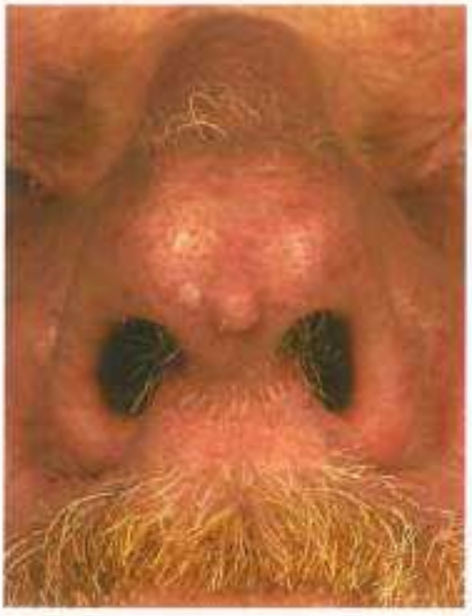


Fig. 9.77 Tricholemmoma. The lesion is a small warty flesh-coloured papule on the nose.

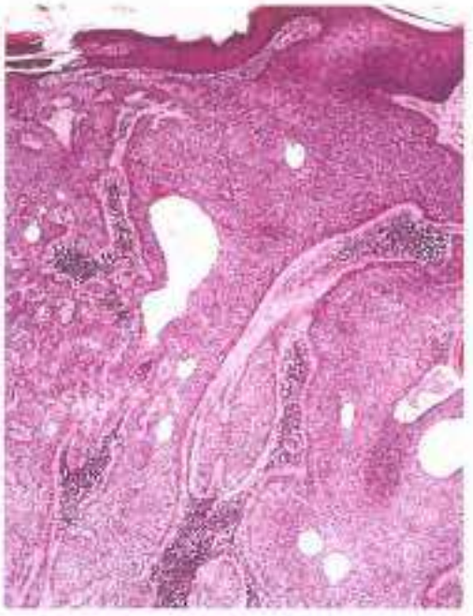


Fig. 9.78 Tricholemmoma. The tumour, which is composed of multiple discrete lobules, originates from the overlying epidermis.

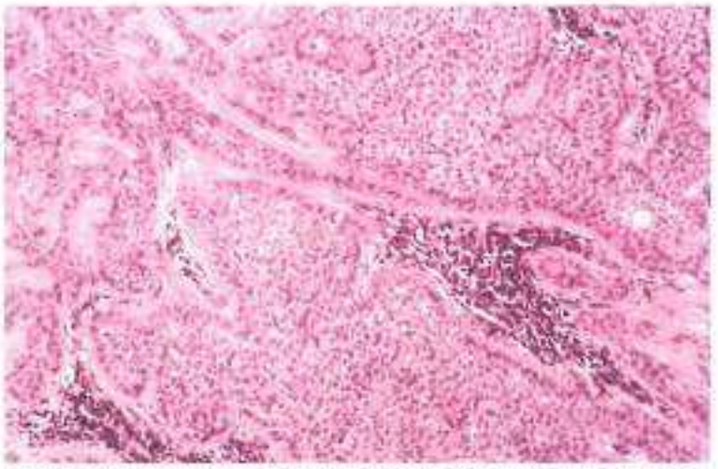


Fig. 9.79 Tricholemmoma. The tumour cells are uniform and show cytoplasmic vacuolation owing to the presence of glycogen. The lobules are surrounded by a narrow rim of hyalinized condensed connective tissue.

peripheral nuclear palisading. The tumour cells frequently have a clear appearance because of the presence of glycogen in the cytoplasm (Fig. 9.79).

Management

Single lesions are usually mistaken for a basal cell carcinoma and are excised. The association with Cowden's syndrome makes the trichilemmoma an important cutaneous marker of malignancy.

BIRT–HOGG–DUBÉ SYNDROME

A rare autosomal dominant hamartomatous proliferation of the mesenchymal and epithelial components of the pilar complex; they are associated with renal tumours and lung cysts but occasionally occur as a solitary lesion.

Aetiology

The Birt–Hogg–Dubé syndrome (syn. multiple *fibrofolliculomas*) is a triad of fibrofolliculomas, trichodiscomas and acrochordons. Fibrofolliculomas are benign neoplasms of the fibrous root sheath of the hair follicle with an associated proliferation of the infundibular portion of the outer epithelial root sheath. A trichodiscoma (indistinguishable from a fibrofolliculoma clinically) is a proliferation of the fibrovascular component of the hair disc (haarscheibe). It is an autosomal dominant condition of variable expressivity and usually presents in the third decade of life. The gene is mapped to chromosome 17p11.2. It encodes folliculin, a tumour suppressor gene. It is associated with renal tumours and lung cysts which give rise to pneumothoraces.

Clinical Features

Symptoms

Fibrofolliculomas are asymptomatic lesions on the face and scalp.

Morphology

Fibrofolliculomas are small, flesh or pale yellow-coloured papules (Fig. 9.80).

Distribution

Fibrofolliculomas are found on the cheeks, forehead, neck and scalp and also on the back, chest and in the popliteal and antecubital fossae.

Histopathology

Fibrofolliculomas are benign proliferations of the perifollicular fibrous and external root sheaths. The hair follicle is cystically dilated and contains

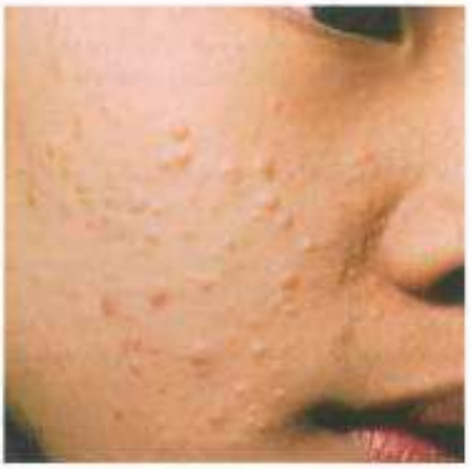


Fig. 9.80 Multiple fibrofolliculomas. Multiple lesions occur with trichodiscomas and acrochordons in the Birt–Hogg–Dubé syndrome associated with familial renal cancer.

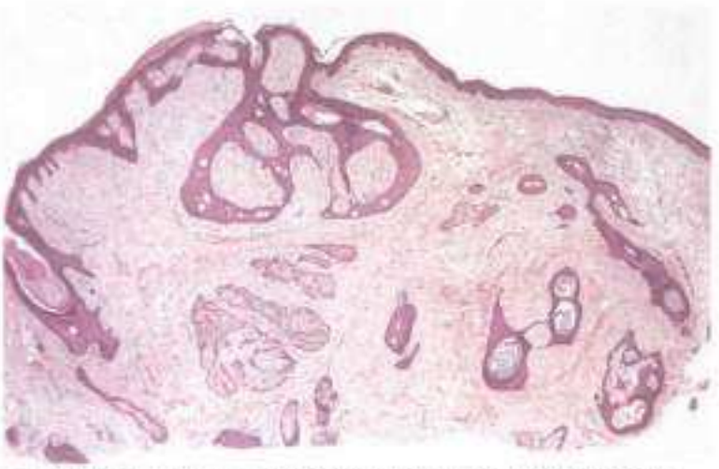


Fig. 9.81 Fibrofolliculoma. The hair follicles are cystically dilated and there is a distinctive proliferation of the outer root sheath epithelium, seen in the upper mid-field.

keratinous debris or a hair shaft (Fig. 9.81). This is surrounded by a well-defined area of loose connective tissue containing fine collagen and elastic fibres and excess hyaluronic acid.

Management

Solitary fibrofolliculomas may be excised. Various ablative destructive procedures may be tried for multiple ones. The importance of the condition is that it is a cutaneous marker for malignant disease.

CALCIFYING EPITHELIOMA OF MALHERBE

A common hamartoma of the hair matrix that may calcify (pilomatrixoma).

Clinical Features

Symptoms

A firm or hard painless lump, often on the face.

Morphology

A small, solitary nodule (Fig. 9.82) with a characteristic firm to hard consistency, often lobulated which may be slightly yellow in colour (Fig. 9.83).

Distribution

Face (especially cheeks; Fig. 9.84), neck and upper limbs.

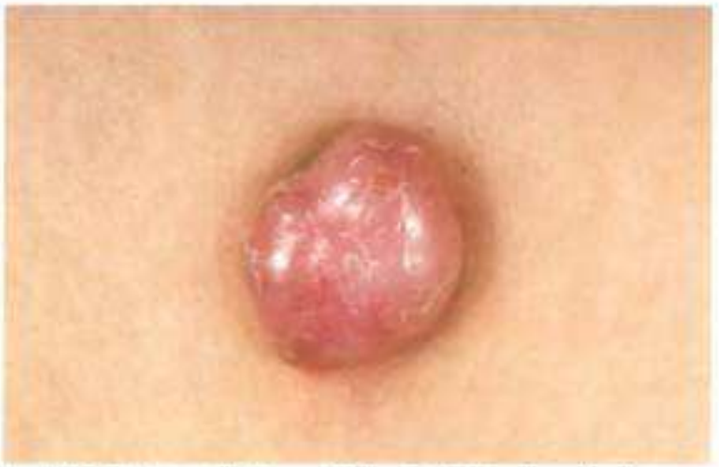


Fig. 9.82 Calcifying epithelioma of Malherbe. The lesion is a solitary firm or hard papule or nodule with a pink and often yellow tinge. It was present on the front of the shoulder. (Courtesy of Dr Elisabeth Higgins.)

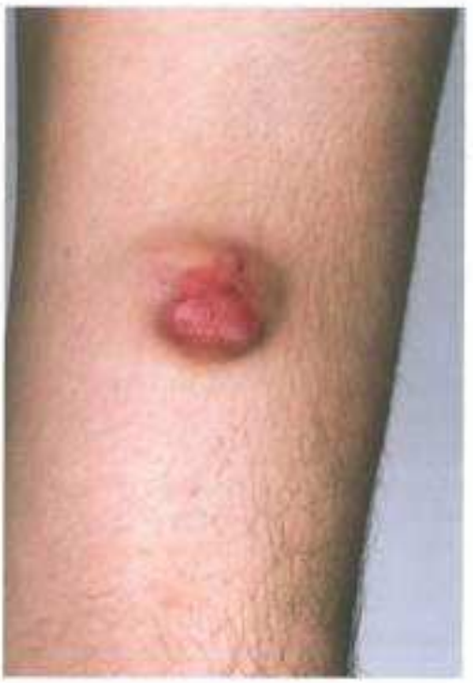


Fig. 9.83 Pilomatrixoma. The lesion is a firm red nodule with a yellow tinge and the diagnosis may be suspected clinically prior to excision.

Histopathology

This is a tumour of follicular origin situated within the dermis and sometimes subcutaneous fat. It has a dual but inter-related population of cells. In early lesions, small, uniform cells predominate that consist of regular, oval basophilic nuclei with scanty cytoplasm. While these cells may focally undergo squamous differentiation, more typically they 'mature' into so-called 'ghost' cells, particularly in older lesions and consist of eosinophilic sheets in which the faint outline of pre-existent epithelial cells may be seen (Fig. 9.85). Giant cells are very common and are often located about the edges of the islands of ghost cells. Despite the name, calcification is present in only a minority of patients (Fig. 9.86). These tumours are also associated with marked chronic inflammation and scarring.

Management

It is benign but usually requires excision for cosmetic reasons and because, rarely, malignant change has been reported. Occasionally multiple lesions are present. It only occasionally occurs in black skin.

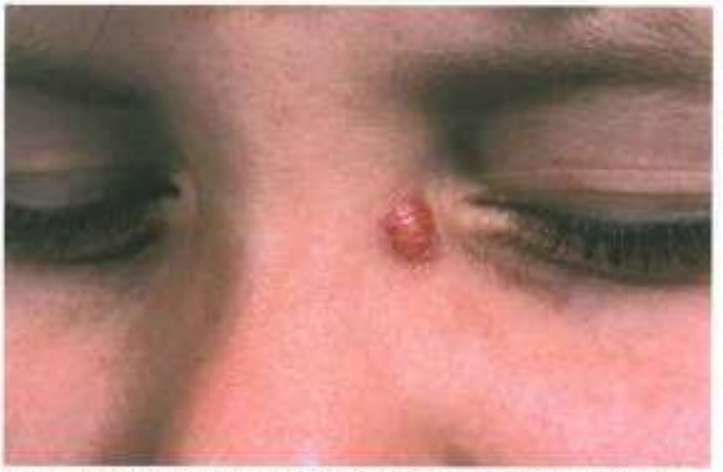


Fig. 9.84 Calcifying epithelioma of Malherbe. The lesion is firm or hard in consistency. It may have a slightly yellow colour. Children are most prone to this lesion.

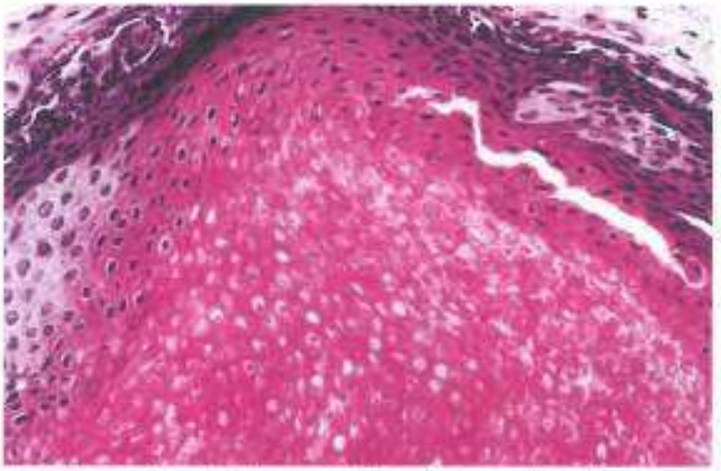


Fig. 9.85 Calcifying epithelioma of Malherbe. Numerous 'ghost' cells are present with intensely eosinophilic cytoplasm. Only nuclear shadows are visible.

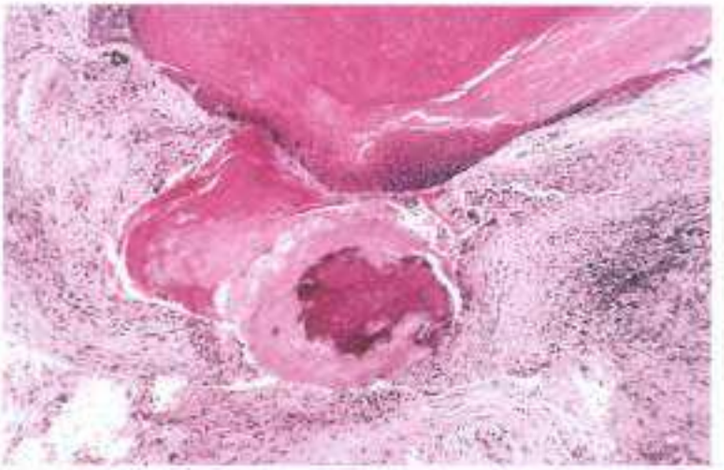


Fig. 9.86 Calcifying epithelioma of Malherbe. Calcification is seen in the lower part of the field, adjacent to the main nodule. Note the scarring and chronic inflammatory changes that surround the lesion.

Fig. 9.87 Senile sebaceous hyperplasia. Multiple yellow umbilicated papules occur on the face. They are common and despite its name may occur from the thirties onwards.

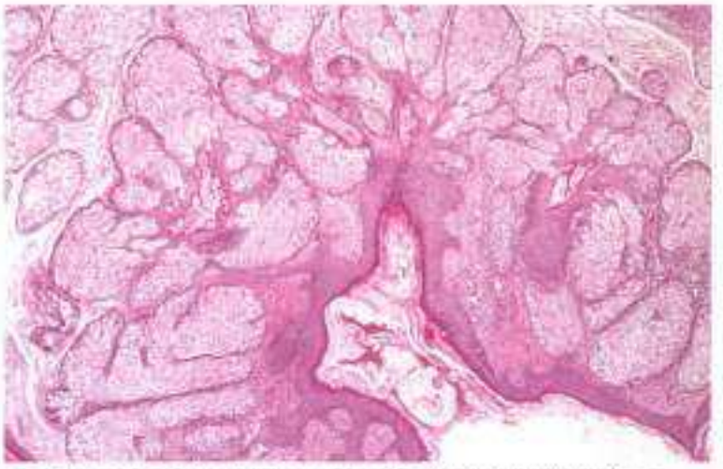


Fig. 9.88 Senile sebaceous hyperplasia. Numerous, mature hyperplastic sebaceous glands are present.

Sebaceous gland tumours

SENILE SEBACEOUS HYPERPLASIA

A small yellow dimpled papule on the face composed of numerous mature hyperplastic sebaceous glands.

Clinical Features

Symptoms

Asymptomatic small lesions on the face.

Morphology

Yellow dome-shaped papules with a central depression (Fig. 9.87).

Distribution

The lesions occur on the forehead and cheeks.

Histopathology

There are hyperplastic mature sebaceous glands that communicate with the surface by a dilated, debris-containing duct (Fig. 9.88).

Management

The papules are occasionally mistaken clinically for a basal cell carcinoma, but their appearance really is quite characteristic. They are harmless but can be cauterized. They are common in organ transplant patients taking ciclosporin.

SEBACEOUS ADENOMA

A rare benign tumour of the sebaceous cells with varying degrees of differentiation in the elderly. Multiple lesions occur in the *Torre–Muir syndrome*.

Aetiology

The solitary sebaceous adenoma occurs in either sex and more usually in the elderly. Multiple lesions occur with other sebaceous neoplasms (sebaceous carcinoma, Fig. 10.117 and sometimes lesions with the architecture of keratoacanthomas, but composed of sebaceous glands (sebo-acanthomas). This condition, known as the *Torre–Muir syndrome*, is dominantly inherited and presents in the fifth decade with gastrointestinal polyposis and colorectal cancer (especially adenocarcinoma) and of the genitourinary tract and breast cancer, and haematological malignancies. It is a subset of hereditary non-polyposis coli cancer (Lynch) syndrome due to a mismatch repair gene abnormality. These genes are responsible for maintaining accurate DNA replication. Defects permit increased accumulation of errors. Tumours show changes in the lengths of chromosomal microsatellites as they replicate.

Clinical Features

Symptoms

A tumour that is usually asymptomatic but may ulcerate.

Morphology

It has a yellow colour and sometimes a warty surface.

Distribution

Sebaceous adenoma occurs most commonly on the face (Fig. 9.89) or scalp, but occasionally elsewhere (Fig. 9.90). It may occur as a subtle periocular yellow plaque along the eyelid margin.

Histopathology

It is a multilobular tumour composed of small basophilic sebaceous cells peripherally with larger cells in which the cytoplasm contains fat globules.

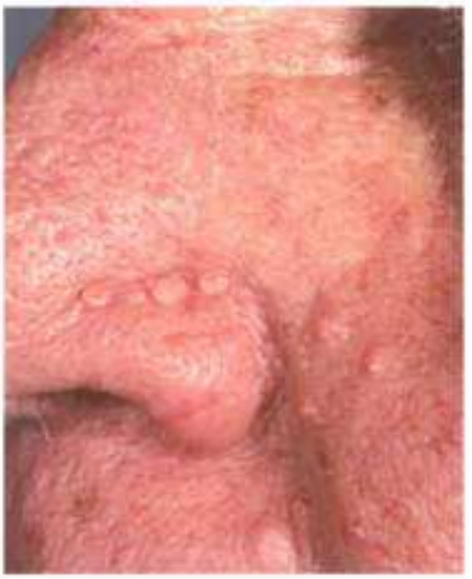


Fig. 9.89 Sebaceous adenoma. Multiple sebaceous neoplasms occur in the Torre–Muir syndrome associated particularly with gastrointestinal polyposis and malignancy. (Courtesy of Dr Genevieve Osborne and the late Dr J. Cream.)

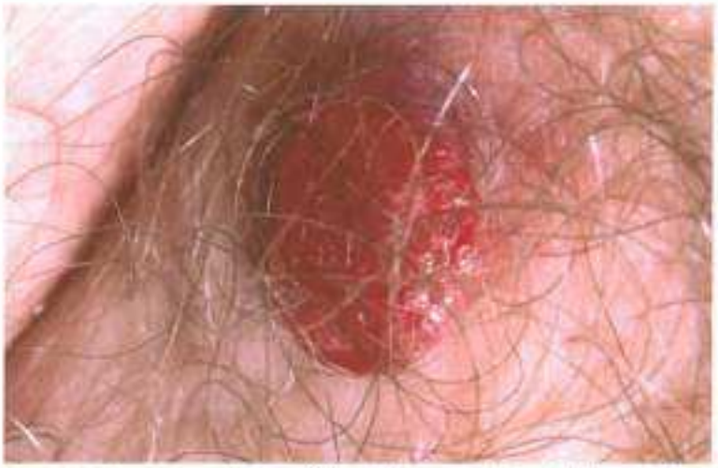


Fig. 9.90 Sebaceous adenoma. Solitary lesions occur in the elderly, particularly on the face, although this one was in the groin. (Courtesy of the late Dr J. Cream.)

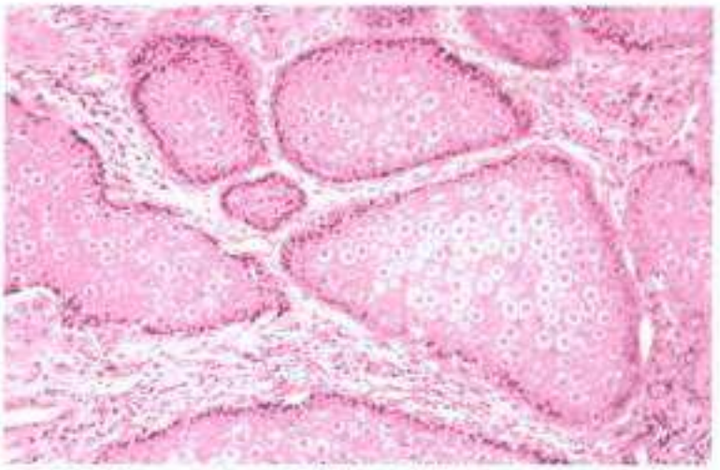


Fig. 9.91 Sebaceous adenoma. This is a multilobular tumour composed of small basophilic sebaceous cells peripherally with larger cells centrally containing fat globules in their cytoplasms. (Courtesy of the late Dr J. Cream.)

There may be cystic spaces lined with a thin layer of the eosinophilic material (Fig. 9.91), similar to that lining the ducts of the sebaceous gland.

Management

Solitary tumours should be excised because they are not easy to distinguish from neoplastic lesions. The Torre–Muir syndrome should be considered when multiple sebaceous adenomas are present.

Fibrous tissue tumours

HYPERTROPHIC SCARS AND KELOIDS

Hypertrophic scars and keloids are hyperproliferative responses of connective tissue to trauma resulting from an imbalance between collagen synthesis and lysis. A hypertrophic scar is confined to the area of trauma whereas a keloid spreads beyond this and has a worse prognosis.

Aetiology

They develop as a consequence of abnormal responses of the skin to a variety of stimuli, which includes inflammation, infection (including chickenpox, Fig. 9.92) and trauma, especially burns. Surgical procedures in certain sites – the chin, neck, shoulders, upper trunk, back and sternum – are often complicated by hypertrophic or widened scars despite excellent technique. Acne, even quite minor, may result in keloids on the sternum, back or shoulders. The tendency may be inherited. Black races are particularly prone, for example after ear piercing and secondary to ingrowing hairs around the neck, back of the scalp and if the whole head is shaven, throughout the scalp (Fig. 9.93).

Keloid fibroblasts are hyporesponsive to mediators that are normally inhibitory to fibroblasts and have marked mutations in their gene for p53. This gene arrests growth and apoptosis following injury to DNA, particularly from ultraviolet light. Similar mutations occur in squamous cell carcinoma. It may be that these mutations disregulate the normal repair sequence following injury and the proliferative phase of healing continues unabated.

Clinical Features

Symptoms

Both hypertrophic scars and keloids give rise to an unsightly scar.

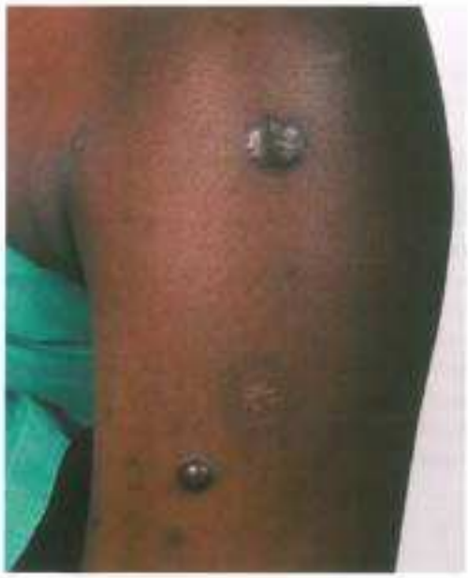


Fig. 9.92 Keloids. These occur most commonly in black skin, often after a trivial injury including acne and, in this case, chickenpox.

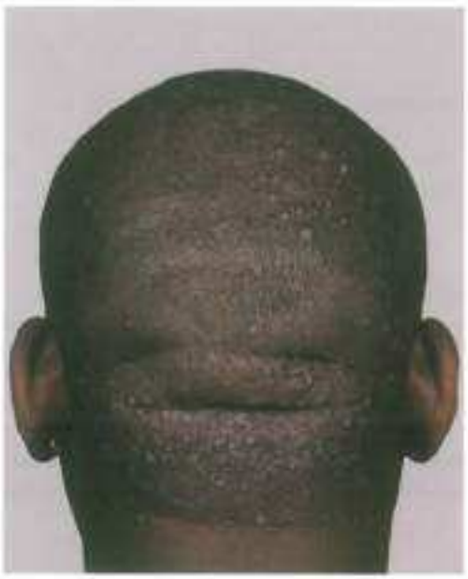


Fig. 9.93 Keloids. Firm papules may become widespread throughout the scalp following shaving the head which may then result in ingrowing hairs, subsequent folliculitis and small keloids.

Fig. 9.94 Keloids. The lesions are most common in black skins. They may result from minor injury, skin disorders (especially acne and chickenpox) or arise spontaneously.

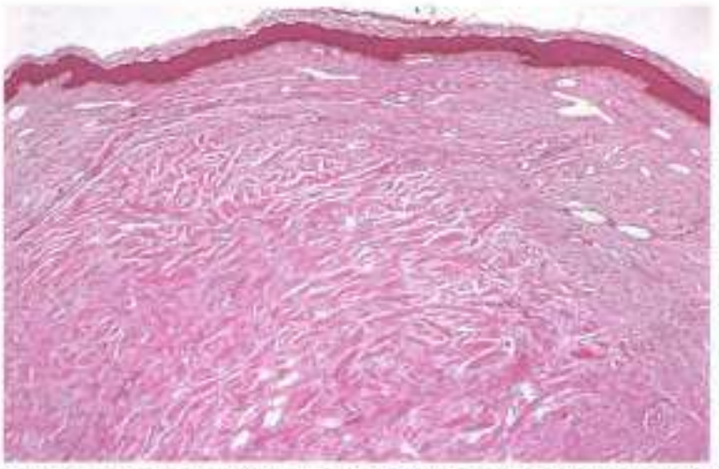


Fig. 9.95 Keloid. The epidermis is unremarkable. The dermis is greatly expanded by broad bundles of dense, acellular fibrous tissue. Note the superficially located ectatic blood vessels.

Fig. 9.96 Nuchal keloids. Firm papules occur on the back of the scalp secondary to folliculitis in black skin. They may become confluent and result in hair loss.

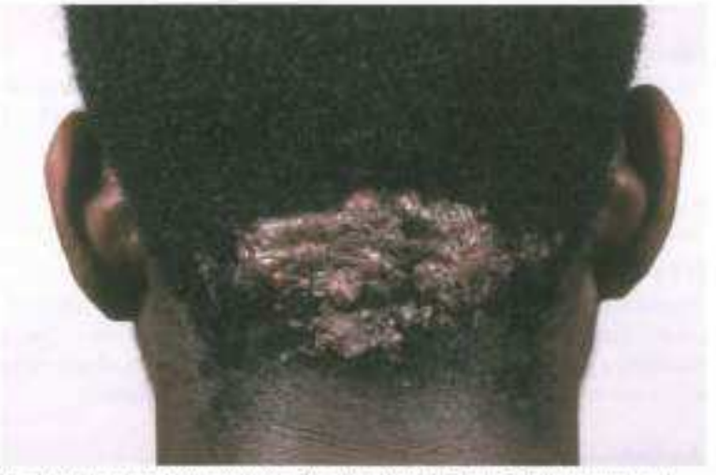


Fig. 9.97 Keloids. Management is fraught with difficulties. Surgery may result in recurrence of the lesions in a much more pronounced manner than prior to therapy.

Morphology

They are raised, firm and have a smooth shiny surface (Fig. 9.94).

Distribution

They may occur anywhere following an injury.

Histopathology

Both hypertrophic scars and keloids are composed of dense fibrous tissue, but the latter consists predominantly of broad bundles of hyalinized collagen (Fig. 9.95).

Management

They may be disappointing to treat. Corrective surgery is frequently followed by recurrence, and the resultant scarring may be greater in size (Figs 9.96 and 9.97). Immediate radiotherapy following excision of the keloid may occasionally be successful (Figs 9.98 and 9.99). Local compression garments may be tried.

Intralesional triamcinolone may be helpful for small lesions, particularly for hypertrophic scars. It is best to use a 1 cm^3 syringe (i.e. a small-bore syringe with a wide-bore needle) so that maximum pressure can be exerted. Tapes impregnated with steroids (for example, fludroxycortide [flurandrenolone]) are useful. They may be applied to the hypertrophic scar and left in position for the whole day, during which time the steroid is slowly released into the scar.

Cultured epithelial allografts have been used to treat extensive recalcitrant keloids. A 1 cm^2 piece of epidermis is taken from the thigh and keratinocytes are cultured. These are then applied at 2 weeks to the site of removal of the keloid and good results have been reported several months later.

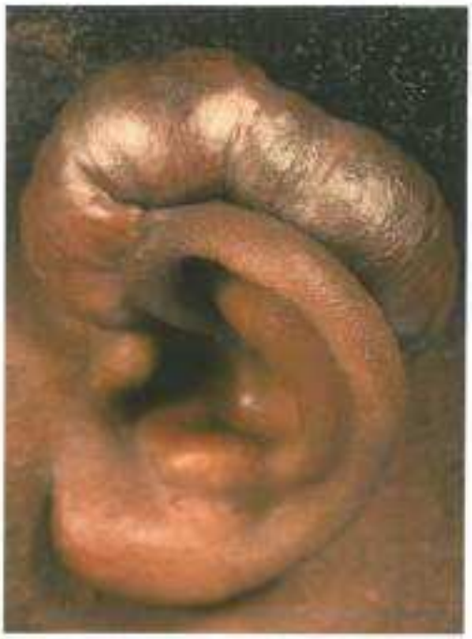


Fig. 9.98 Keloids. Keloids may be very unsightly and arise from trivial injury such as ear piercing.

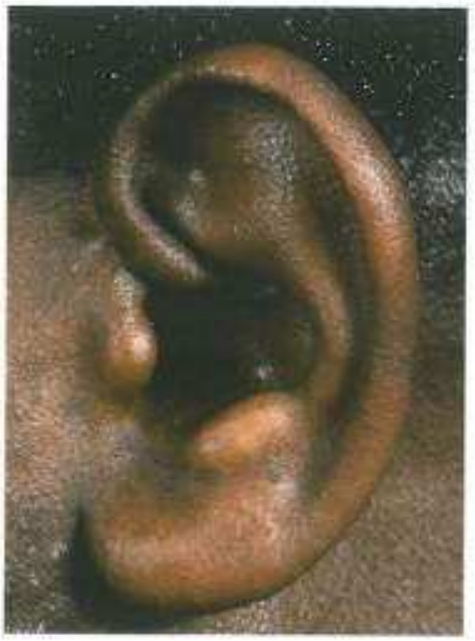


Fig. 9.99 Treatment of Keloids. Management is difficult. Occasionally immediate radiotherapy following excision of the keloid (Fig. 9.98) is successful.

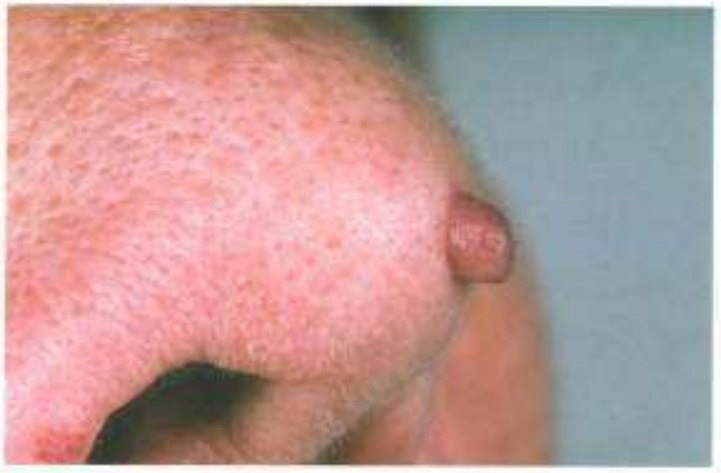


Fig. 9.100 Fibrous papule of the nose. A solitary flesh-coloured papule is present on the nose of an adult. They may occur elsewhere on the face. They are benign but may be readily shaved off the skin.

Fibrohistiocytic tumours

Fibrous and fibrohistiocytic proliferations include cutaneous angiofibromas which have widely different clinical presentations but similar histopathologies. Examples are:

- **Fibrous papule** of the nose (Fig. 9.100)
- **Multiple nasal fibromas** (Fig. 9.101) associated with tuberous sclerosus (Ch. 20)
- **Periungual fibromas** (Fig. 9.102) also associated with tuberous sclerosus

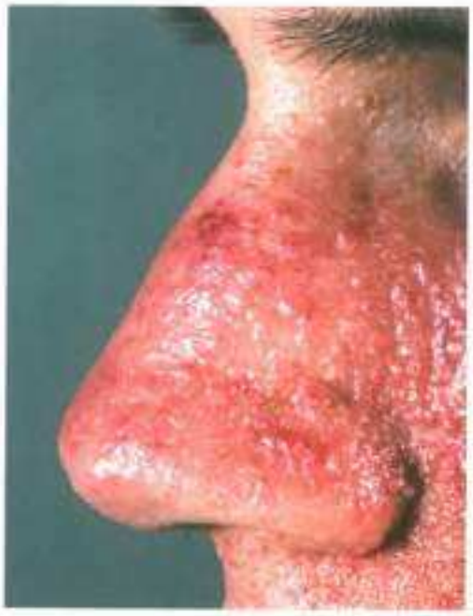


Fig. 9.101 Tuberous sclerosis. Firm flesh-coloured or pink papules occur particularly around the nose. Pathologically the lesions are angiofibromas which occur in several minor clinical conditions, but here represent a potentially serious inherited neurocutaneous disorder.

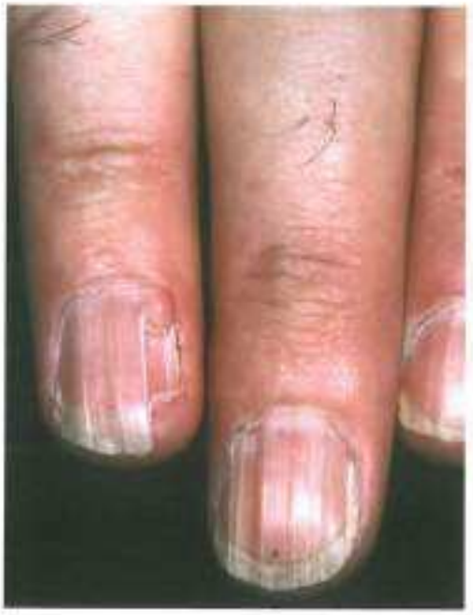


Fig. 9.102 Periungual fibroma. These fibromas resembling garlic cloves are diagnostic of tuberous sclerosis. Pathologically they are angiofibromas.

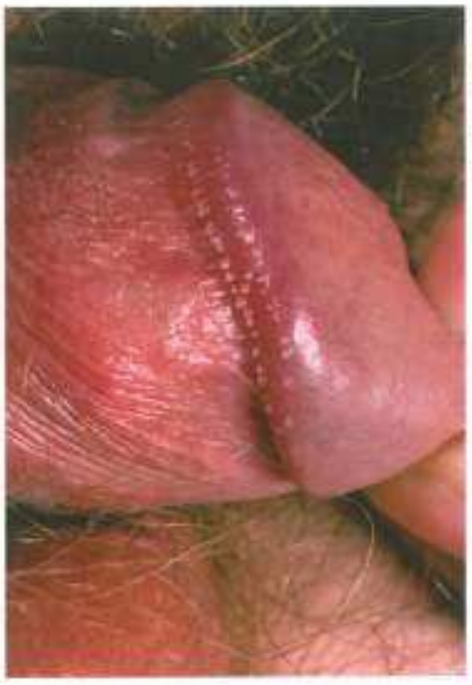


Fig. 9.103 Pearly penile papules. A myriad of small white papules occurs along the corona. They are of no significance except when mistaken for viral warts.

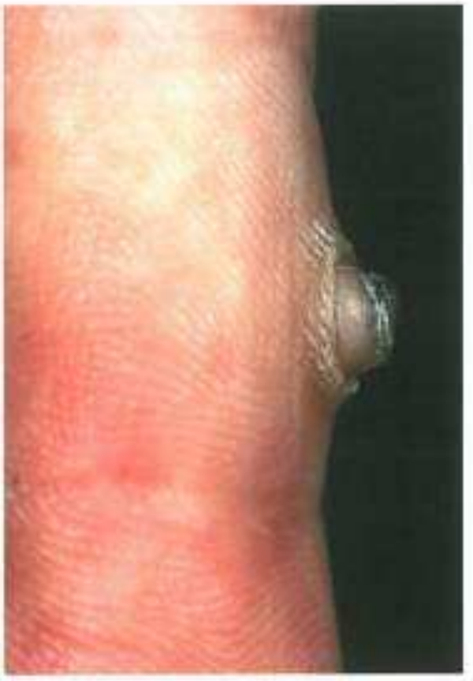


Fig. 9.104 Acquired digital fibrokeratomas. There is a somewhat keratotic exophytic papule with a collarette of skin at its base on the side of the finger. They are acquired in adult life but may be mistaken for an accessory digit (present from birth) or wart. They may be shaved away from the skin.

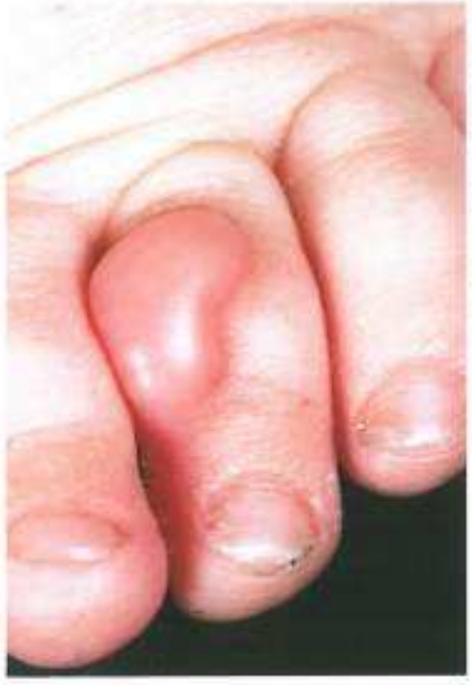


Fig. 9.105 Infantile digital fibroma. A distinctive firm smooth flesh-coloured nodule is present on the dorsolateral side of the toe in an infant. They occur on the digits but spare the thumb and big toe and usually resolve spontaneously in childhood. They represent a proliferation of spindle-shaped myofibroblasts.

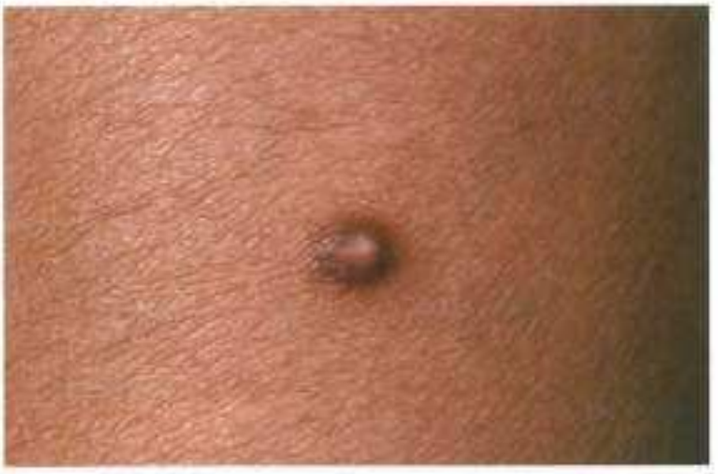


Fig. 9.106 Dermatofibroma. The centre is often paler than the surround. This may dimple on lateral pressure. The lesion is quite firm.

- **Pearly penile papules** (Fig. 9.103).

Other types include

- **Dermatofibromas** (described here)
- **Acral fibrokeratomas** (Fig. 9.104)
- **Infantile digital fibroma** (Fig. 9.105).

DERMATOFIBROMA

A common, probably reactive, skin tumour that occurs especially on the legs.

Aetiology

It is possible that a dermatofibroma (histiocytoma, sclerosing haemangioma) represents a reaction to a long-forgotten insect bite. They are often multiple, occur most commonly on the lower legs, and patients often remark that they are prone to insect bites. It is a reactive process that involves fibroblasts, endothelial cells and histiocytes.

Generalized eruptive histiocytomas is a rare entity, probably related to the non-Langerhans' cell histiocytoses.

Clinical Features

Symptoms

An unsightly, sometimes tender, lump within the skin.

Morphology

A raised papule (Fig. 9.106) or nodule with a smooth surface. It is quite firm and can be gripped between the finger and thumb and moved within

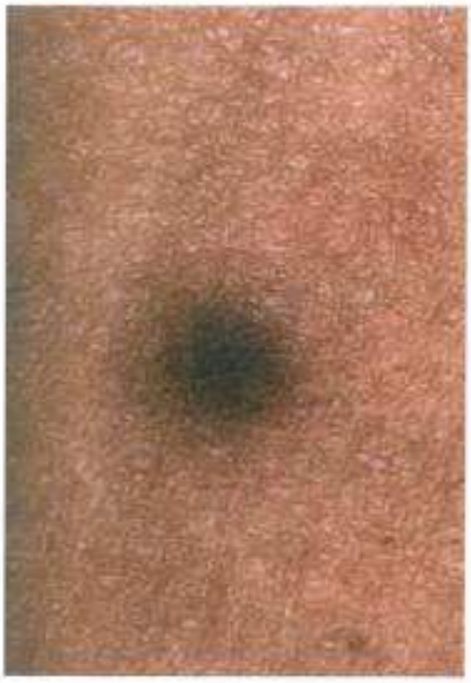


Fig. 9.107 Dermatofibroma. The lesion is a firm, pigmented papule that is attached to the overlying skin. It is relatively mobile within the skin.

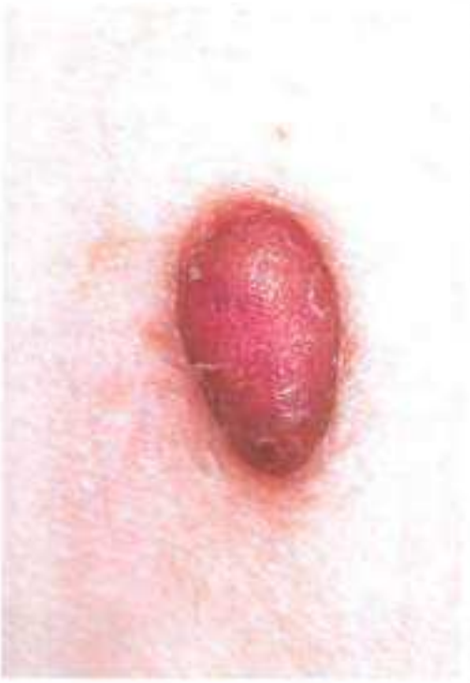


Fig. 9.108 Dermatofibroma. Occasionally the lesion is quite large and may raise the possibility of dermatofibrosarcoma protuberans. The firm nature and smooth surface of the nodule may aid pre-excision diagnosis.

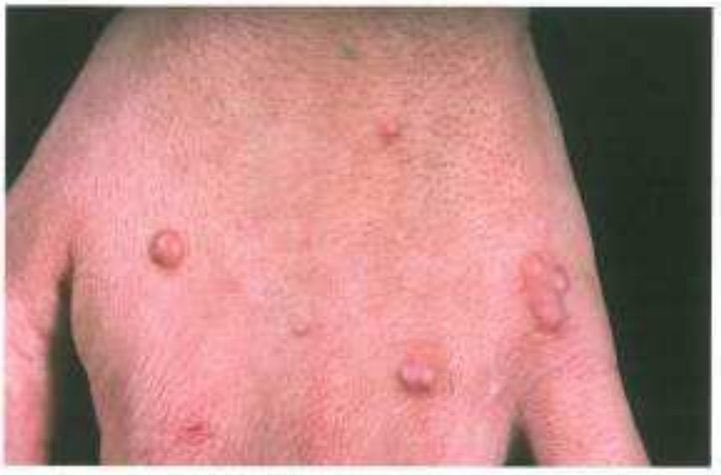


Fig. 9.109 Multiple dermatofibromas. Although patients may have several lesions scattered on the limbs, it is unusual to have multiple eruptive papules as here. They have been seen in immunosuppressed patients.

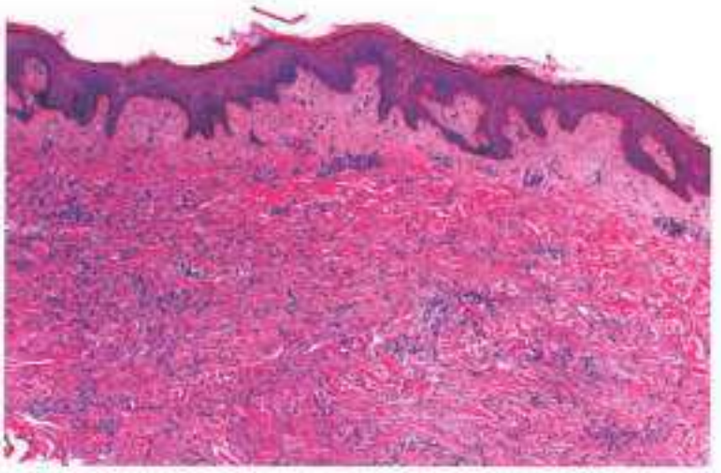


Fig. 9.110 Dermatofibroma. The dermis is largely replaced by a connective tissue neoplasm involving the superficial aspect of the subcutaneous fat. The spindle cells are dispersed in an abundant collagenous stroma. (Courtesy of Dr Jon Salisbury.)

the skin, but it is adherent to the overlying skin. A characteristic feature is the 'dimple' sign such that the tumour will indent or dimple on lateral pressure with the thumb and index finger. It varies in colour, being red-brown, brown or sometimes very dark brown (Fig. 9.107). Larger lesions (Fig. 9.108) may occur. Rarely patients have many lesions (Fig. 9.109).

Distribution

Anywhere on the body, especially the limbs.

Histopathology

It has a variable appearance depending upon the relative proportions of fibroblasts, histiocytes and collagen. It is a spindle-cell neoplasm that predominantly occupies the reticular dermis and is often separated from an acanthotic epidermis by a Grenz-zone of sparing (Fig. 9.110). The lateral margins of the tumour are typically indistinct and blend imperceptibly into the adjacent tissues. It is composed of variably cellular, interlacing fascicles of spindle cells with plump, elongated nuclei and indistinct cytoplasmic margins. Foamy histiocytes and multinucleate giant cells may be additional features. When there is a histiocytic predominance, the tumour is sometimes called a *fibrous histiocytoma*. Some tumours that are excessively vascular and accompanied by marked haemosiderin deposition are known as *sclerosing haemangiomas*.

Management

It may be excised for diagnostic or cosmetic reason, although excision of those on the lower limbs is often followed by a less than perfect scar.

JUVENILE XANTHOGRANULOMA

An uncommon regressing tumour of infancy which may be solitary or multiple.

Aetiology

Although previously known as *naevoxanthoendothelioma*, there are no naevus or endothelial cells present. It is the most common form of non-Langerhans' cell histiocytosis (Birbeck granules are absent on electron microscopy and markers specific for Langerhans' cells are negative). It presents either during the first year of life or occasionally in early adult life. It is much more common in females. It rarely has extracutaneous associations in the mouth, eye, lung, liver, testes and elsewhere. It may be associated with café-au-lait patches and neurofibromatosis NF1 and juvenile chronic myelogenous leukaemia.

Clinical Features

Symptoms

Yellow spots, often on the head.

Morphology

Single or multiple, small or large, orange (Fig. 9.111) or yellow papules or nodules (Fig. 9.112).

Distribution

Usually on the head and neck (Fig. 9.113) but may occur anywhere.

Histopathology

An irregular heterogeneous collection of inflammatory cells (Fig. 9.114) that includes lipid-laden histiocytes, eosinophils and giant cells particularly of the Touton type.

Management

It regresses spontaneously in most children between the age of 3 and 6 years leaving behind pigmentary, atrophic or anetodermic changes in 50%. The lesions are quite benign and most children are otherwise perfectly healthy. Ophthalmic examination is essential because juvenile xanthogranuloma may be associated with glaucoma.

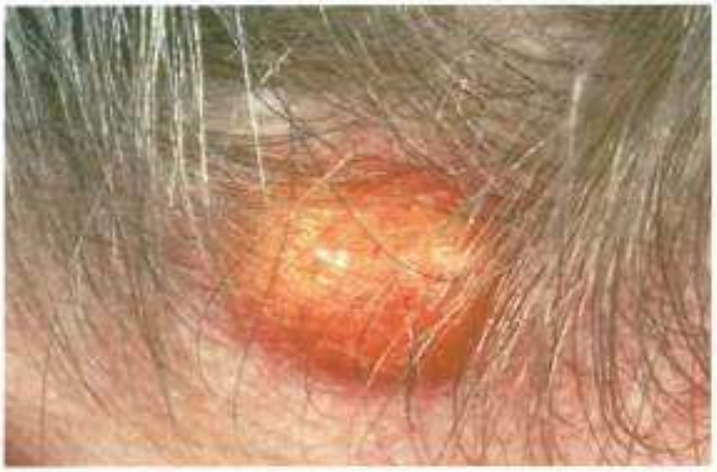


Fig. 9.111 Juvenile xanthogranuloma. The lesion is yellow. It may be solitary or multiple. It normally develops before the age of 6 months and involutes spontaneously.

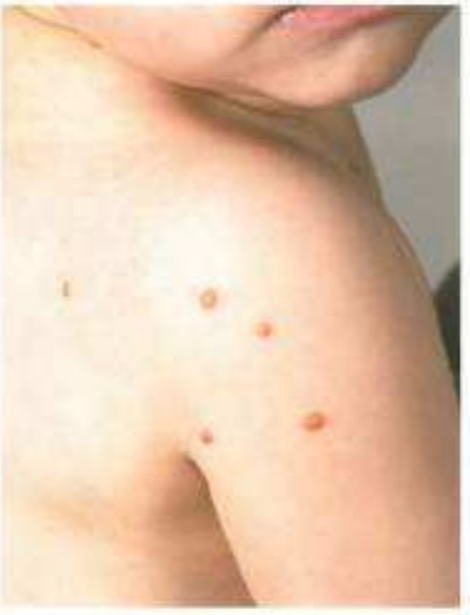


Fig. 9.112 Juvenile xanthogranuloma. There are often multiple yellowish papules in infancy, which ultimately regress.

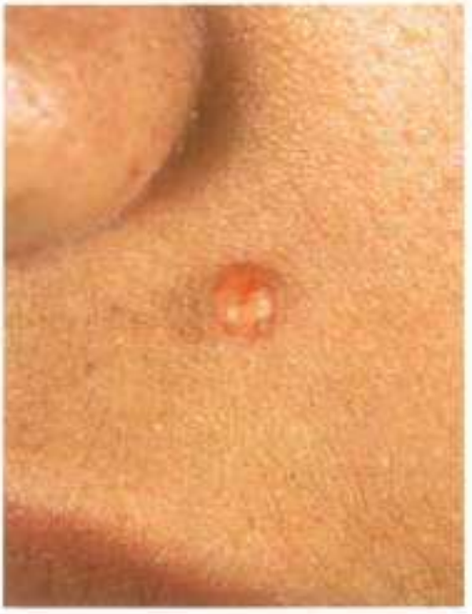


Fig. 9.113 Juvenile xanthogranuloma. Solitary lesions may occur in adults. They are a yellow colour often with surface telangiectasia.

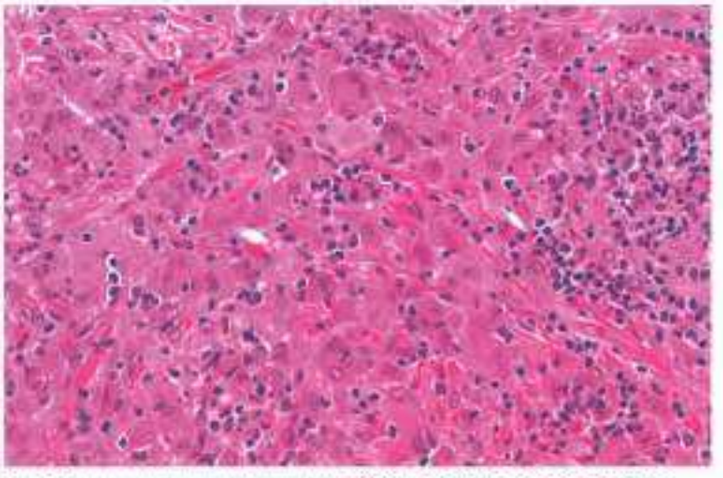


Fig. 9.114 Juvenile xanthogranuloma. Scattered multinucleated histiocytes are present amongst lymphocytes, proliferating vessels and scattered eosinophils. Later stages are accompanied by Touton giant cells.
(Courtesy of Dr Jon Salisbury.)

Tumours of nervous tissue

NEUROFIBROMA AND NEURILEMMOMA

They are both benign tumours of nerve sheath origin.

Clinical Features

Symptoms

Both neurofibroma and neurilemmoma give rise to lumps on the skin.

Morphology

Neurofibromas are flesh coloured (Fig. 9.115), soft or firm, vary greatly in size and occur anywhere on the integument. The lesions can often be invaginated with the fingertip (the 'buttonhole' sign). Solitary lesions are often mistaken for cellular naevi. Neurilemmoma (schwannoma) are usually solitary (Fig. 9.116), painless, solid tumours of variable size that arise from peripheral nerves. Both occur as multiple tumours in association with neurofibromatosis (Fig. 9.117).

Distribution

Both neurofibroma and neurilemmoma may occur anywhere.

Histopathology

The neurofibroma is a discrete but unencapsulated tumour. It is composed of interlacing fascicles of Schwann cells that have irregular, wavy, elongated nuclei. Variable amounts of collagen and mucopolysaccharides are also present. Small nerve fibres may be found coursing through its substance (Fig. 9.118).

The neurilemmoma is rounded and encapsulated. It consists of plump spindle cells, which show a marked tendency to palisading, and irregularly scattered spindly or stellate cells in an abundant loose myxoid stroma. Also present are chronic inflammatory cells and hyalinized blood vessels.

Management

Solitary lesions may be excised.

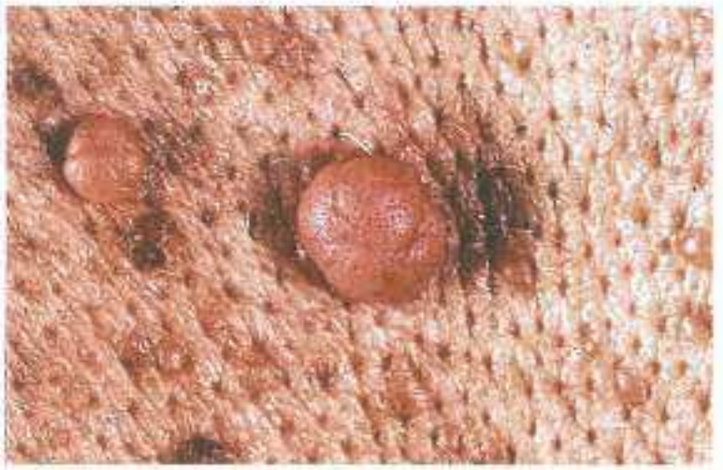


Fig. 9.115 Neurofibroma. The nodule is flesh coloured and may be either soft or firm. A characteristic finding is that it can be invaginated with the tip of a finger.

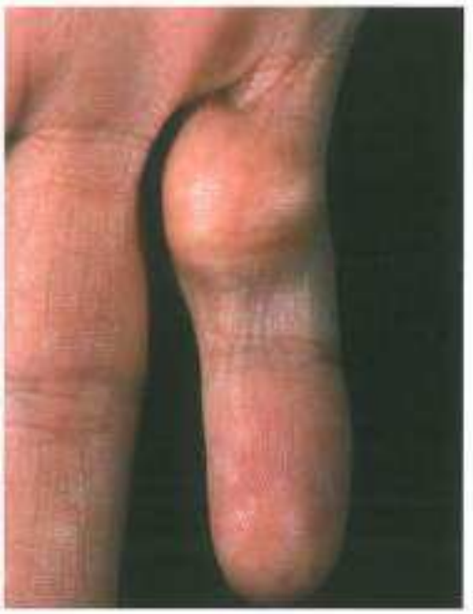


Fig. 9.116 Neurilemmoma. The Schwannoma is solitary, painless, flesh coloured and of variable size. It arises from a peripheral nerve.

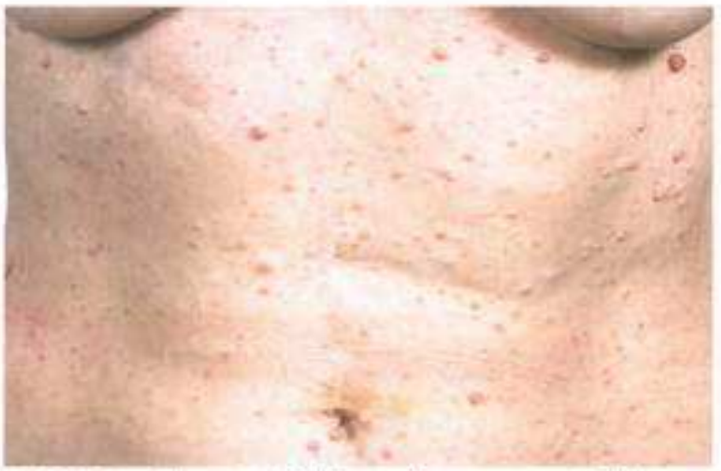


Fig. 9.117 Neurofibromatosis. Multiple neurofibromas are present. This is von Recklinghausen's disease. Café-au-lait macules and axillary freckling will be found elsewhere on the body.

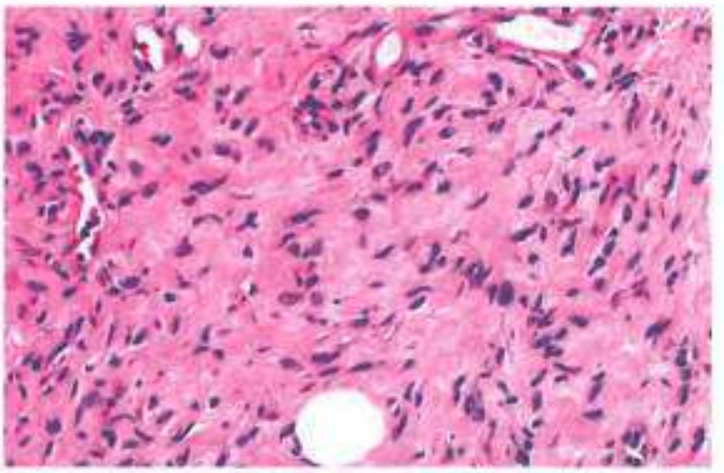


Fig. 9.118 Neurofibroma. The tumour is composed of eosinophilic connective tissue containing wavy, spindle-shaped nuclei. Scattered mast cells are a frequent finding. (Courtesy of Dr Jon Salisbury.)

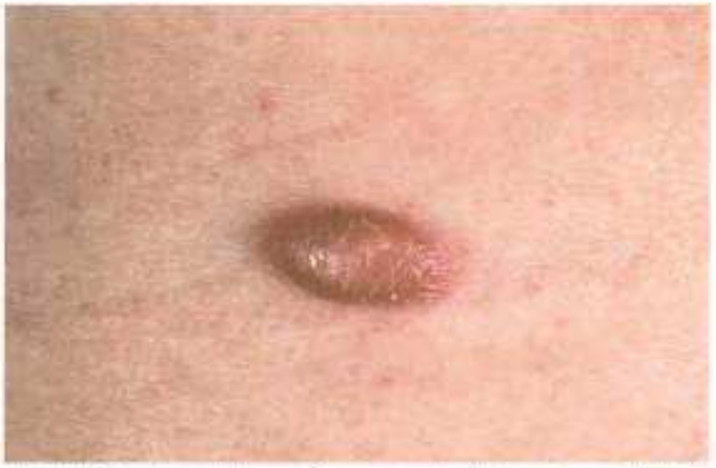


Fig. 9.119 Granular cell tumour. Pre-excision clinical diagnosis may be difficult. The lesion is nodular and may be smooth surfaced or hyperkeratotic.

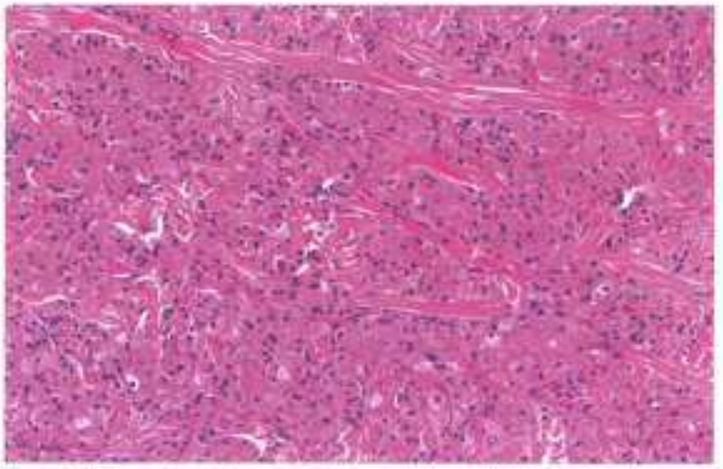


Fig. 9.120 Granular cell tumour. The tumour is formed of large cells with an eosinophilic granular cytoplasm. There may be secondary hyperplasia of the overlying epidermis. (Courtesy of Dr Jon Salisbury.)

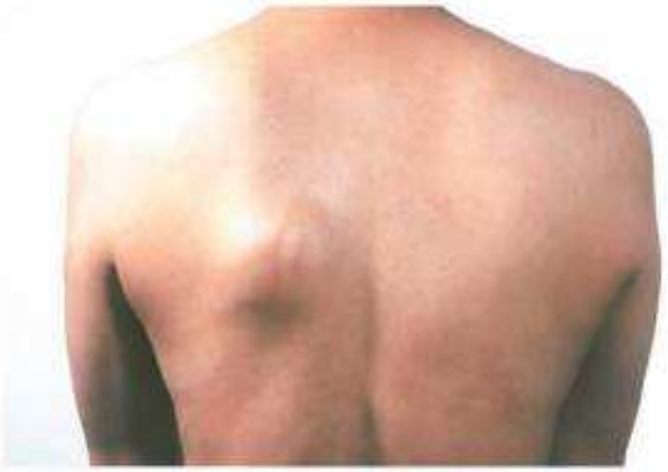


Fig. 9.121 Lipoma. The tumour is soft and sometimes lobulated. It is flesh coloured and quite benign.

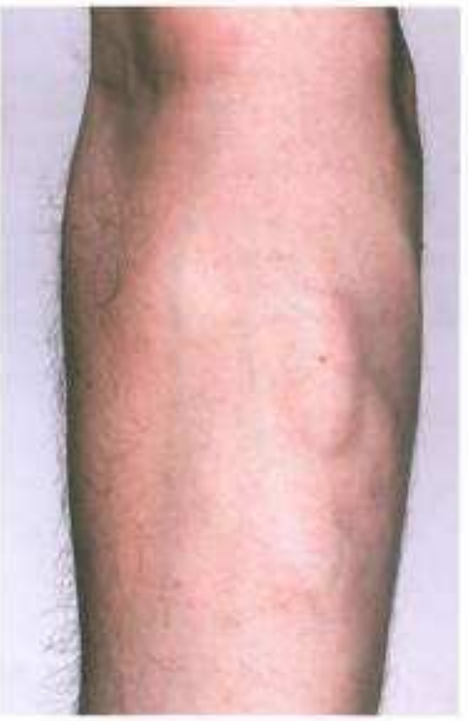


Fig. 9.122 Lipomas. Multiple lesions are quite frequent on the limbs and are usually familial. They are harmless but very occasionally are associated with neurofibromatosis, Proteus or Gardner's syndrome and lipomas in other organs.

GRANULAR CELL TUMOUR

A rare tumour possibly arising from Schwann cells on the head and neck.

Clinical Features

Symptoms

The granular cell tumour appears as an asymptomatic lump(s).

Morphology

This may be quite variable, making clinical diagnosis difficult; they may be smooth surfaced or hyperkeratotic nodules (Fig. 9.119).

Distribution

Anywhere on the skin and not uncommon on the tongue.

Histopathology

The tumour has pale-staining polygonal cells containing eosinophilic granules (Fig. 9.120).

Management

The lesion should be adequately excised to establish the diagnosis. Multiple lesions are occasionally present and viscera may be involved.

Tumours of adipose tissue

LIPOMA

A common benign tumour of adipose cells.

Aetiology

Lipomas may be solitary or multiple (and familial) but usually have no particular significance. They are twice as common in males, and present in early adult life. However they are associated with neurofibromatosis, Proteus syndrome, Gardner's syndrome and visceral lipomas in the lungs, gastrointestinal or genitourinary tract. If a lipoma overlies the lumbar region, spina bifida may be present.

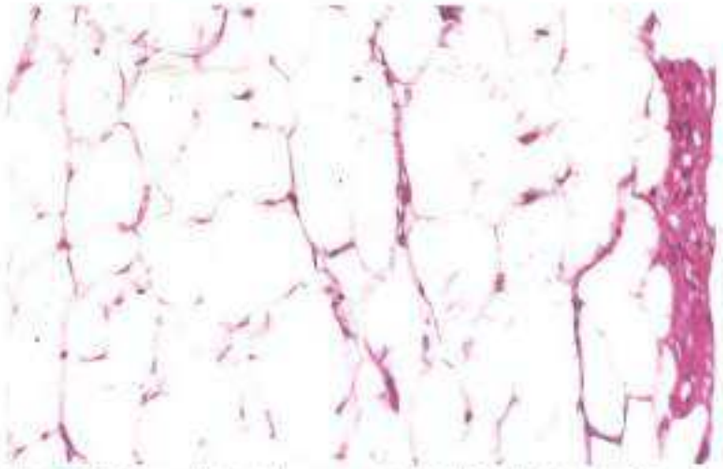


Fig. 9.123 Lipoma. The lesion is composed of adult fat cells. A portion of the capsule is seen on the far right.

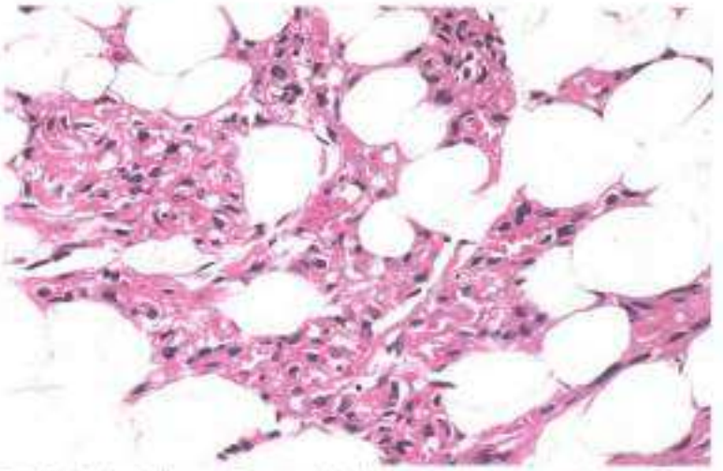


Fig. 9.124 Angiolipoma. There are foci of small proliferating vessels in addition to the fat cells.

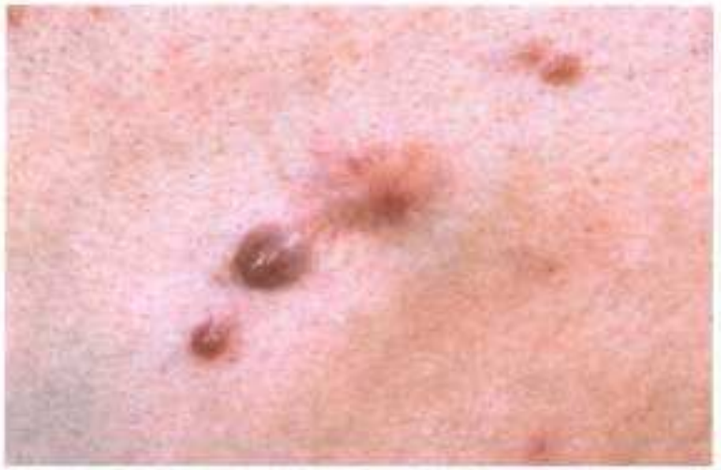


Fig. 9.125 Leiomyoma. The lesions are multiple, red-brown, painful and often distributed in a linear manner. Many are familial and associated with uterine myomas.

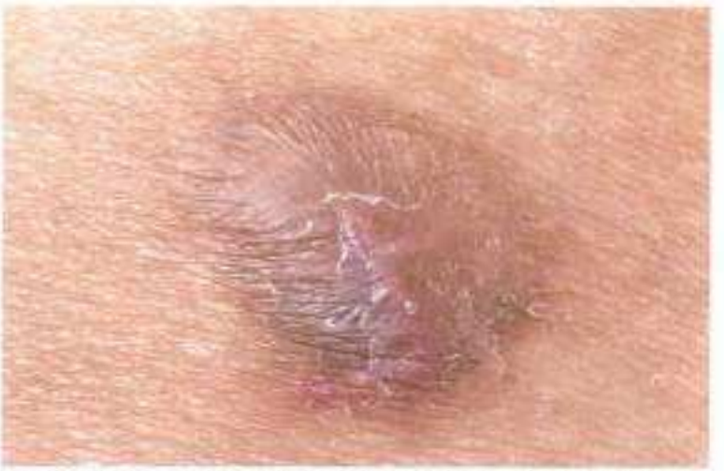


Fig. 9.126 Nipple leiomyoma. This lesion arose from the smooth muscle of the areola.

Clinical Features

Symptoms

Asymptomatic large subcutaneous swellings.

Morphology

Lipomas are soft, sometimes lobulated and have a normal flesh-coloured skin surface that is freely moveable over the tumour (Fig. 9.121). They vary in size. Angiolipomas are a vascular variant that may be tender and painful and have a red/blue discoloration.

Distribution

Commonly on the arms (Fig. 9.122), back of the neck and trunk.

Histopathology

The lipoma is a discrete lesion that is composed of mature adult fat cells (Fig. 9.123). Sometimes there is an excessive vascular component, known as angiolipoma (Fig. 9.124).

Management

Lipomas are largely of cosmetic significance but are too extensive for surgery to be practical for all lesions. However, single lesions may be excised. Ultrasonography may aid accurate diagnosis.

Tumours of muscular tissue

SMOOTH MUSCLE TUMOURS (LEIOMYOMA)

A benign tumour derived from the smooth muscle associated with hair follicles, blood vessels, genitalia or nipples.

Clinical Features

Symptoms

Usually painful.

Morphology and distribution

- **Arrector pili muscle leiomyoma** It is derived from the arrector pili muscle and commences in youth, particularly on the limbs or neck. The lesions are often multiple (Fig. 9.125); they are red, pink or brown in colour, less than 1.5 cm in size and subject to episodic pain, especially precipitated by touch or low temperature, and may contract. Although sporadic segmental tumours do occur, many are familial and are inherited as an autosomal dominant and associated with uterine myomas.
- **Solitary dartoic or nipple leiomyoma** This tumour can occur at any age and is solitary. It is less often painful and arises from the smooth muscle of the genitalia or areola of the nipple (Fig. 9.126).

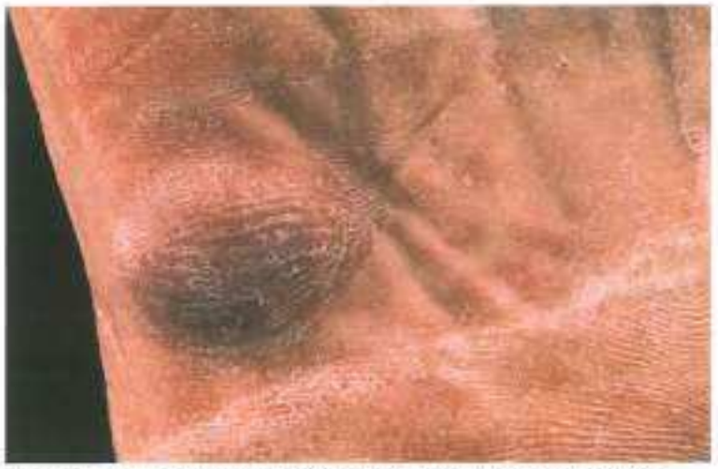


Fig. 9.127 Angioleiomyoma. The lesion is solitary and larger than the other types. The sole of the foot is a common site.

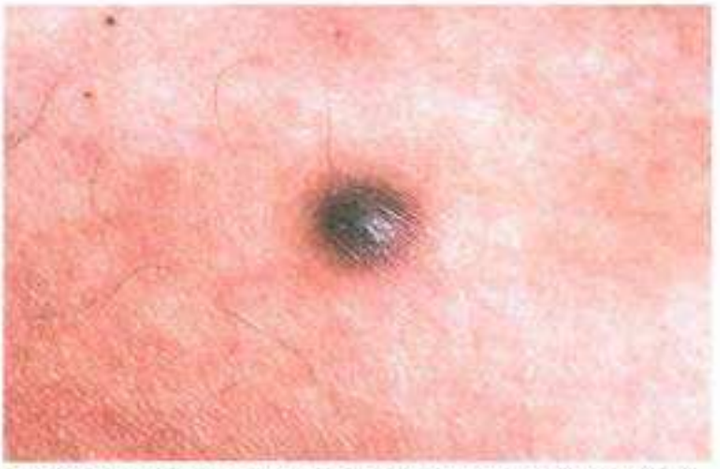


Fig. 9.128 Angioleiomyoma. A small dark papule is present. Diagnosis may be difficult clinically prior to excision, but the clue is that they are often painful.

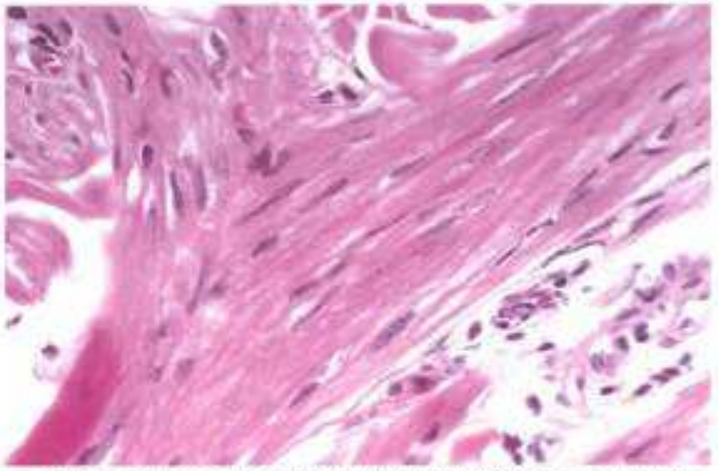


Fig. 9.129 Leiomyoma. The scanning view shows complete replacement of the dermis by broad, interlacing fascicles of eosinophilic spindle cells.

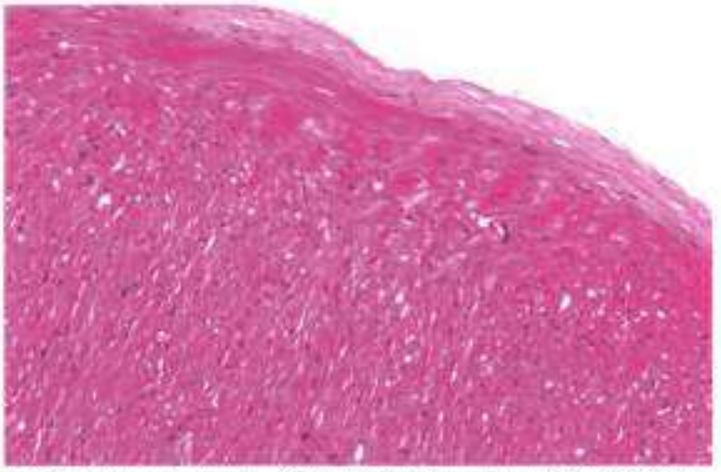


Fig. 9.130 Angioleiomyoma. A fibrous capsule surrounds a mass composed of smooth muscle cells with their characteristically eosinophilic cytoplasm. These tumours are thought to develop from the media of dermal blood vessels. (Courtesy of Dr Jon Salisbury.)

- **Angioleiomyoma** This tumour arises from the muscle coat of the veins. The lesion is solitary (Fig. 9.127); it is found on a limb and is usually larger than the other varieties (Fig. 9.128).

Histopathology

Leiomyomas are composed of interlacing fascicles of smooth muscle cells that are characterized by their elongated, blunt-ended nuclei and abundant eosinophilic cytoplasm (Fig. 9.129). In angioleiomyomas, the cells are distributed around thick-walled blood vessels (Fig. 9.130).

Management

The leiomyoma is one of six skin tumours that are painful. These are memorized by their mnemonic BENGAL (blue rubber bleb naevus, eccrine spiradenoma, neuroma, glomus tumour, angiolipoma and leiomyoma). Solitary lesions may be excised. Leiomyosarcoma (Fig. 9.131) does enter the differential diagnosis.

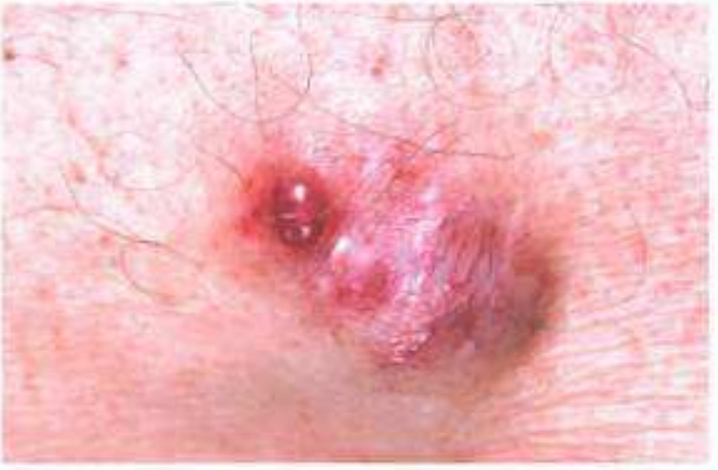


Fig. 9.131 Leiomyosarcoma. This is a recurrent lesion. The red papule at the top of the tumour is characteristic of the original lesion.

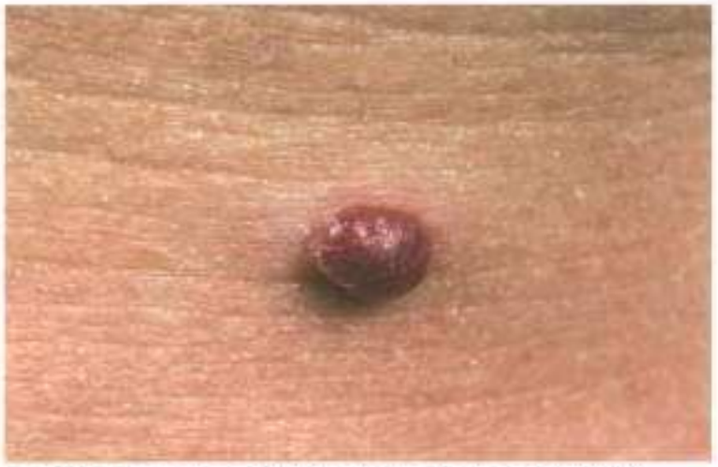


Fig. 9.132 Haemangioma. The solitary haemangioma is a dome-shaped, smooth-surfaced red or sometimes purple papule.

Fig. 9.133 Campbell de Morgan spots. These red macules or papules on the torso are very common and often begin quite early in life. They are harmless.

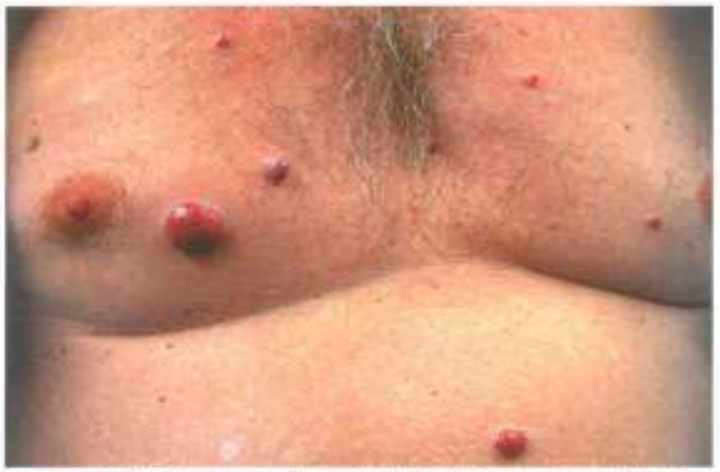


Fig. 9.134 POEMS syndrome. This patient had multiple angiomas, weight loss, fatigue, neuropathy, adult-onset diabetes, hypothyroidism and peripheral edema secondary to myeloma. (With permission from Bolognia JL, Jorizzo JL, Rapini RP. Dermatology, 2e. Elsevier, 2008.)

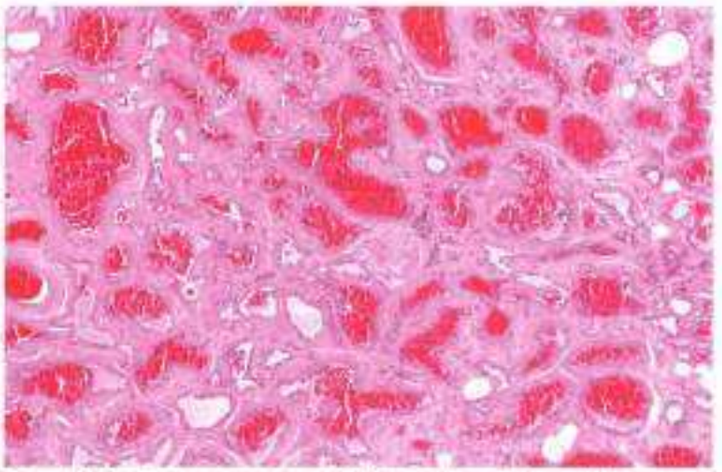


Fig. 9.135 Capillary haemangioma. This benign tumour is formed by numerous anastomosing capillary-sized spaces. Most of the spaces contain red blood cells. (Courtesy of Dr Jon Salisbury.)

Tumours of vascular origin

HAEMANGIOMA (CHERRY HAEMANGIOMA)

A red or purple macule or papule.

Aetiology

It may be solitary (Fig. 9.132) or multiple when they are often known as Campbell de Morgan spots in the UK or cherry haemangiomas in the USA. (Fig. 9.133). They are common but the cause is unknown. They increase in number during pregnancy and tend to subside afterwards. About half the patients with a rare condition known as POEMS syndrome have haemangiomas (Fig. 9.134). The syndrome consists of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy (IgM) and skin disorders. The cutaneous manifestations are hyperpigmentation, hirsutism, Raynaud's phenomenon, scleroderma, acquired ichthyosis, purpura and ulceration.

Clinical Features

Symptoms

A single or multiple asymptomatic red spots.

Morphology and distribution

In senile haemangioma, there are tiny pinpoint red macules, or more obvious, discrete, red smooth-surfaced papules that can occur anywhere on the body.

Histopathology

The lesion is a simple capillary haemangioma (Fig. 9.135).

Management

Usually senile haemangiomas are of no medical significance. They can be excised or cauterized. In POEMS, the haemangioma has a specific

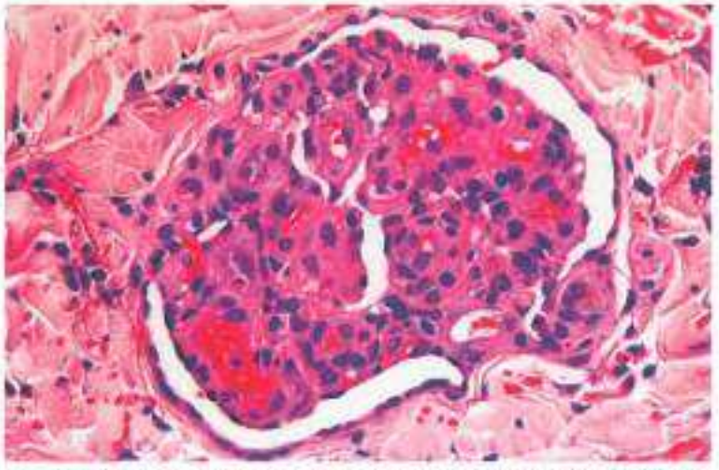


Fig. 9.136 Glomeruloid haemangioma. From a patient with POEMS syndrome. The dermis contains a vascular proliferation consisting of aggregates of capillaries projecting as broad tufts into vascular spaces. These mimic renal glomeruli. (Courtesy of Dr Jon Salisbury.)

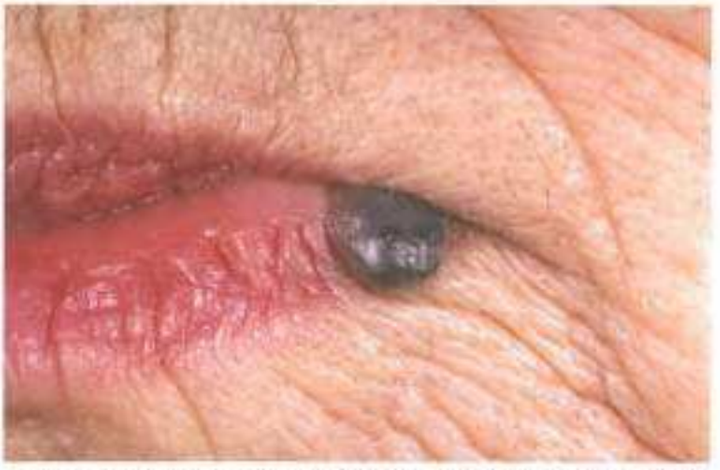


Fig. 9.137 Venous lake. This venous varix is a common benign vascular tumour on the lip in the elderly.

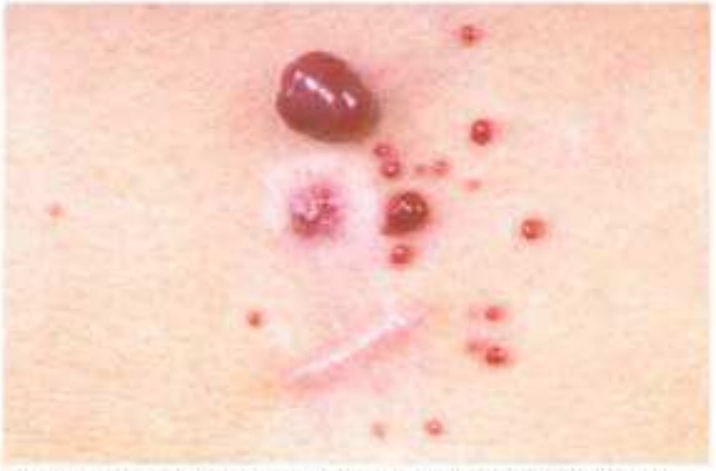


Fig. 9.138 Multiple eruptive pyogenic granulomas. Sometimes following treatment multiple satellite lesions develop around the original pyogenic granuloma. (Courtesy of Dr Michele Clement.)

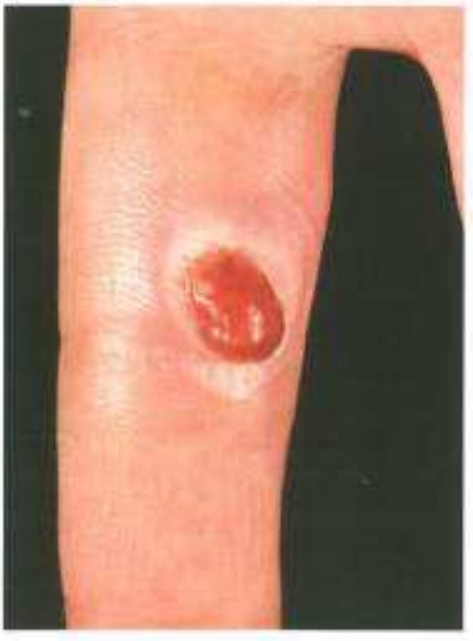


Fig. 9.139 Pyogenic granuloma. The lesion is a red papule or nodule that is friable and bleeds easily. The finger is a common site.

glomeruloid appearance (Fig. 9.136). Venous lakes (Fig. 9.137) occur on the lower lip in the elderly due to venous dilatation. It is lined with a single layer of flattened endothelial cells and a thick wall of fibrous tissue.

PYOGENIC GRANULOMA

A common benign vascular papule occurring in youth, possibly as a response to injury.

Aetiology

A pyogenic granuloma (granuloma telangiectaticum) is a cutaneous vascular proliferation that is one of a heterogeneous group of conditions which includes angiolymphoid hyperplasia (which was formerly known as atypical pyogenic granuloma), bacillary angiomatosis and pseudo Kaposi's sarcoma. The lesion affects both sexes and occurs mostly in children and young adults but may present at any time. It may result from trauma, but many patients have no recollection of any injury. Despite its name, the condition is neither granulomatous in pathology nor pyogenic in origin. Multiple eruptive (Fig. 9.138) and widespread pyogenic granulomas may follow treatment or occur during retinoid therapy. The *epulisis gravidarum* or gingival lesion of pregnancy is identical pathologically to pyogenic granuloma.

Clinical Features

Symptoms

The lesion is sudden in onset and tends to bleed.

Morphology

A friable papule or nodule, red or purple in colour.

Distribution

Anywhere on the skin, including the mucosal surfaces, but they are most common on the fingers (Fig. 9.139), around the nails, on the face and in the scalp (Fig. 9.140).

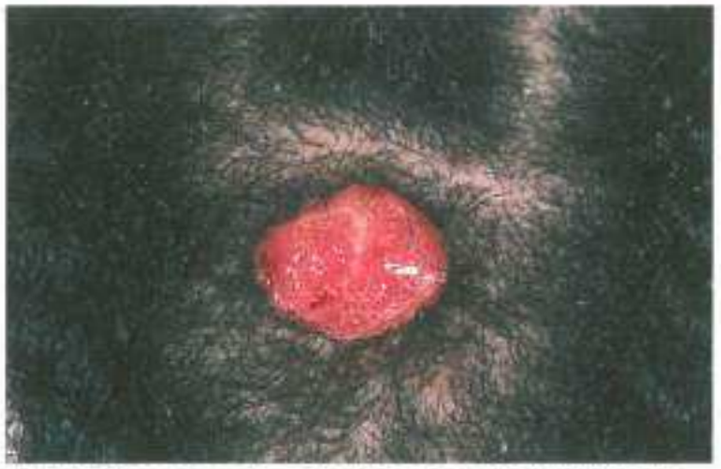


Fig. 9.140 Pyogenic granuloma. The scalp is a common site. The lesion can be removed by curettage under local anaesthesia. Cautery is required to stem the often profuse bleeding.

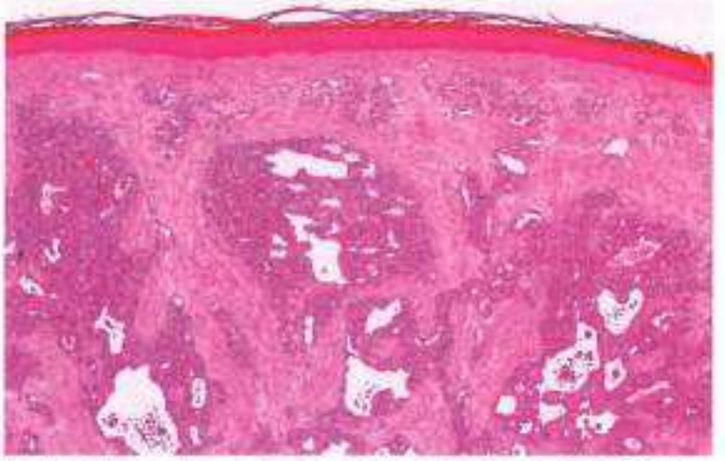


Fig. 9.141 Pyogenic granuloma. This benign capillary haemangioma is formed by numerous anastomosing capillary-sized spaces. These are arranged in a lobular architecture. (Courtesy of Dr Jon Salisbury.)

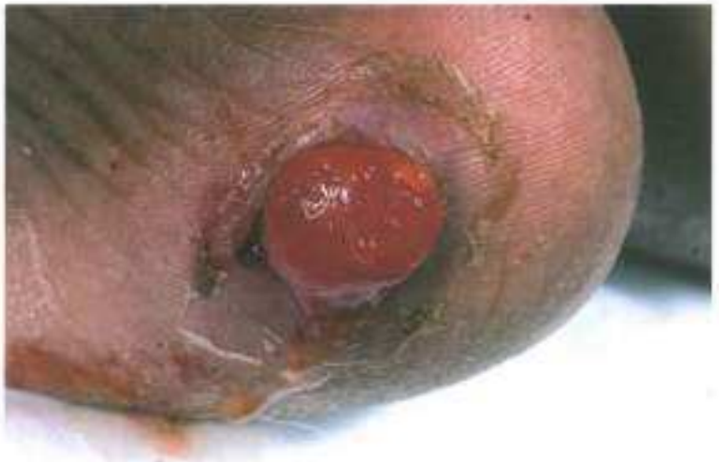


Fig. 9.142 Excess granulation tissue. This may simulate a pyogenic granuloma, but the surface is raw and eroded. This lesion responded to silver nitrate topically.

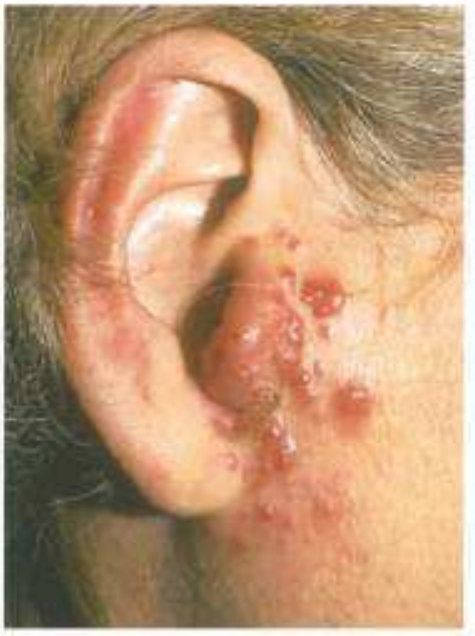


Fig. 9.143 Angiolymphoid hyperplasia with eosinophilia. There are red papules and nodules around the ear. (Courtesy of the late Dr Neil Smith.)

Histopathology

It is a florid expression of granulation tissue of uncertain histogenesis. It is lobulated, often ulcerated and consists of a number of large blood-filled vascular channels from which numerous small capillary vessels arise (Fig. 9.141).

Management

A pyogenic granuloma can be simply removed by curettage and cautery under local anaesthesia. Excess granulation tissue (Fig. 9.142) may resemble a pyogenic granuloma, but the surface is raw and eroded. It responds to applications of silver nitrate.

ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA

A benign proliferation of vascular channels with a surrounding infiltrate of lymphocytes and eosinophils occurring around the ear or hairline in young females.

Aetiology

The cause is unknown although there may be a history of trauma. Deep biopsies often show an arteriovenous shunt, suggesting that it is a reactive hyperplastic process resulting from damage and repair of a vein or artery. It is rare, occurring predominantly in females in the third or fourth decade. It is also known as *atypical pyogenic granuloma* or *epithelioid haemangioma*.

Clinical Features

Symptoms

The lesions may be painful, pruritic or pulsatile.

Morphology

Multiple asymptomatic red and translucent nodules or plaques.

Distribution

The nodules are located in the head and neck region, particularly around the ear (Fig. 9.143) or hairline. Occasionally, there is lymphadenopathy and peripheral blood eosinophilia.

Histopathology

There are well-circumscribed nodules in the dermis or subcutaneous fat, or both, consisting of large numbers of irregular thick blood vessels of various sizes. These vessels are lined by large endothelial cells (Fig. 9.144) with a histiocytoid appearance, meaning that they have large nuclei with abundant eosinophilic cytoplasms that often contain prominent vacuoles. Usually there is an intense eosinophil infiltrate in the surrounding stroma.

Management

Angiolymphoid hyperplasia with eosinophilia is no longer considered to be a late stage of *Kimura's disease*, which it resembles, but which occurs in younger patients, lasts longer and is deeper seated (Fig. 9.145), involving the soft tissues and producing changes without affecting the overlying skin. These patients also have intense peripheral eosinophilia and lymphadenopathy, but Kimura's disease appears to be more of an inflammatory systemic process of unknown origin than a disorder of blood vessels. It occurs in Asian or Oriental males (first described in Japan) and there are massive subcutaneous swellings on the face, particularly around the ear and in the submandibular region and raised levels of IgE. Angiolymphoid hyperplasia with eosinophilia is benign but, unlike other hyperplasias, does not usually regress. Simple excision is often followed by a recurrence unless the arteriovenous shunt is excised. Cryotherapy and laser therapy have their advocates. The tumour is radiosensitive.

Angiokeratomas

Naevoid, congenital and familial disorders (angiokeratoma circumscriptum, angiokeratoma of Mibelli and angiokeratoma corporis diffusum) are dealt with in Chapter 8. Acquired lesions are discussed here.

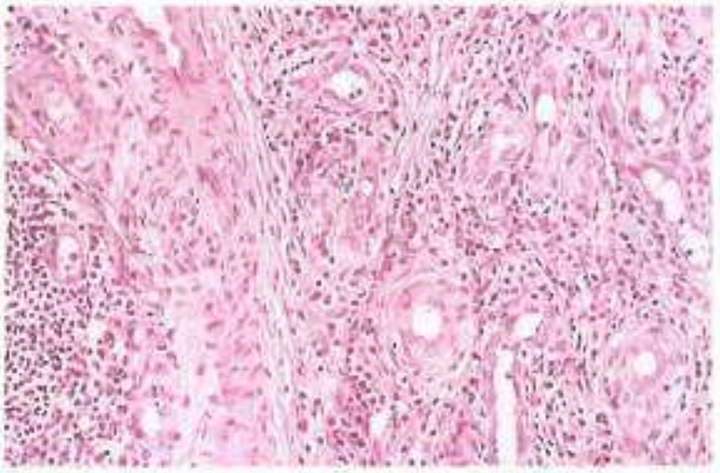


Fig. 9.144 Angiolymphoid hyperplasia with eosinophilia. There are a large number of blood vessels lined by 'epithelioid' endothelial cells. There is usually an intense eosinophilic infiltrate in the surrounding stroma.

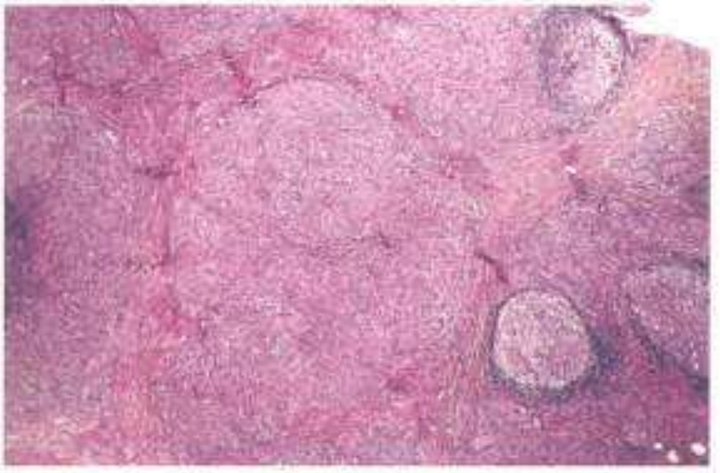


Fig. 9.145 Kimura's disease. There is an inflammatory cell infiltrate with numerous lymphoid follicles, eosinophilic microabscesses and proliferation of endothelial venules.

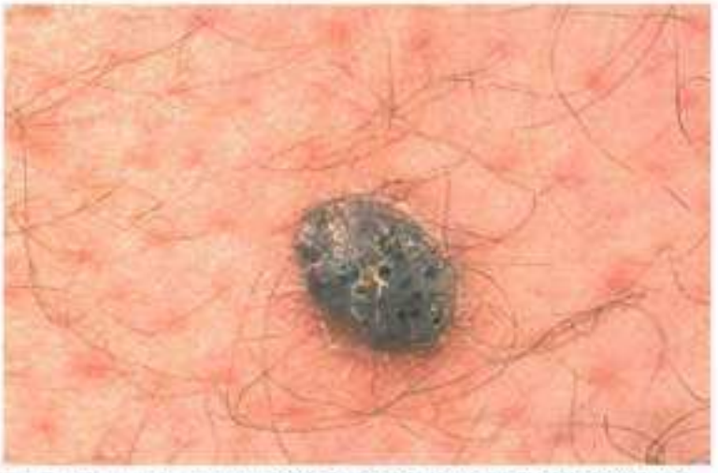


Fig. 9.146 Angiokeratoma. There is a nodule. The warty surface is seen quite clearly. Excision is necessary to establish the diagnosis histopathologically.

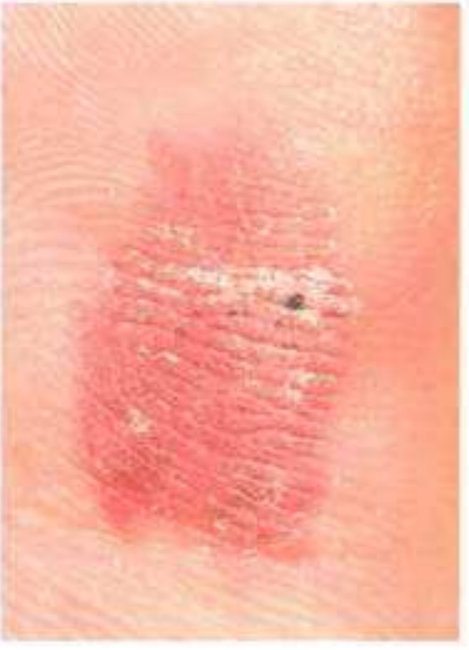


Fig. 9.147 Angiokeratoma. The lesion may sometimes present as a deep red plaque on a limb or the palm or sole.

SOLITARY ANGIOKERATOMA

A benign solitary abnormality of papillary dermal blood vessels that occurs on a limb.

Clinical Features

Symptoms

There may be a sudden enlargement, darkening or bleeding.

Morphology

The morphology is varied but classically it is a deep red nodule (Fig. 9.146) or plaque with a warty surface (Figs 9.147 and 9.148).

Distribution

Angiokeratoma occurs most commonly on the limbs.

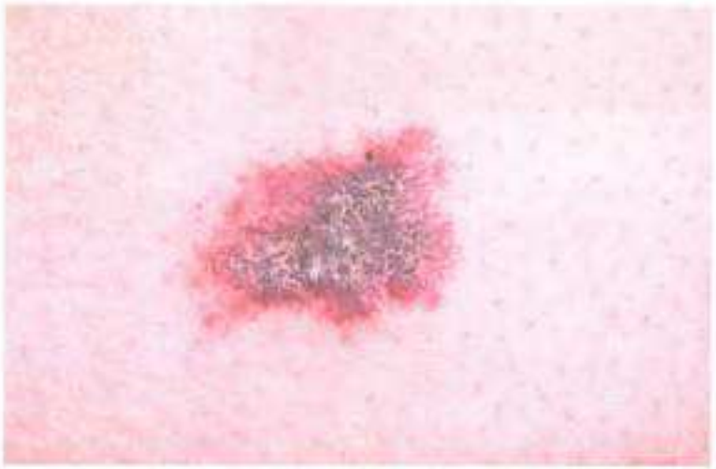


Fig. 9.146 Angiokeratoma. There are typically red and may have a warty surface.

Histopathology

There are dilated thin-walled blood vessels situated within the upper, particularly papillary, dermis, which often appear to be located within the epidermis (Fig. 9.149). There is a variable degree of associated hyperkeratosis.

Management

It occurs in young people of both sexes and needs to be distinguished from a malignant melanoma. It can be excised for histological examination.

ANGIOKERATOMA OF THE GENITALIA

A relatively common benign vascular papular disorder of the genitalia. (Syn. angiokeratoma of Fordyce).

Aetiology

Those occurring in older age groups may be degenerative secondary to local venous hypertension. Others occur in adolescence.

Clinical Features

Symptoms

There are red spots on the genitalia that occasionally itch or bleed.

Morphology and distribution

The angiokeratoma are multiple, small, bright red papules on the scrotum (Fig. 9.150) or labia majora. They may be more extensive.

Management

Angiokeratomas of the genitalia of Fordyce are of no clinical significance except when they occur in a more diffuse form, in which case *Anderson–Fabry disease* (Ch. 8) must be considered in the differential diagnosis. The lesions are benign, and reassurance is all that is usually required. They can be treated with cryotherapy or diathermy.

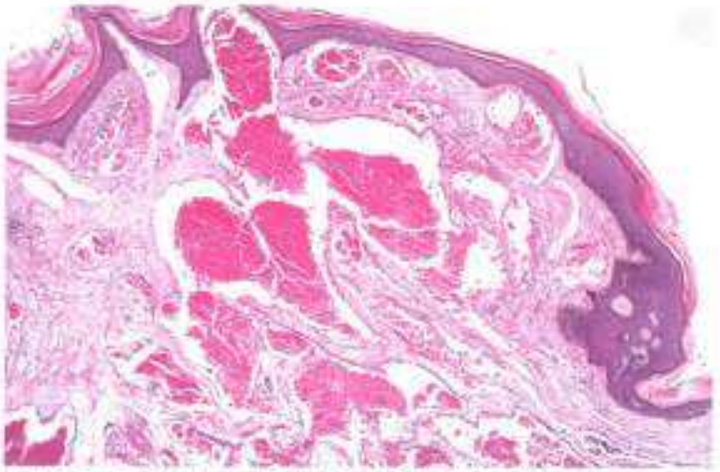


Fig. 9.149 Angiokeratoma. There are conspicuous thin-walled vascular spaces in both the papillary and reticular dermis, with hyperkeratosis overlying the epidermis.

Fig. 9.150 Angiokeratoma of Fordyce. This is a small red papule with a rough surface. Lesions on the scrotum are often multiple and are quite harmless.

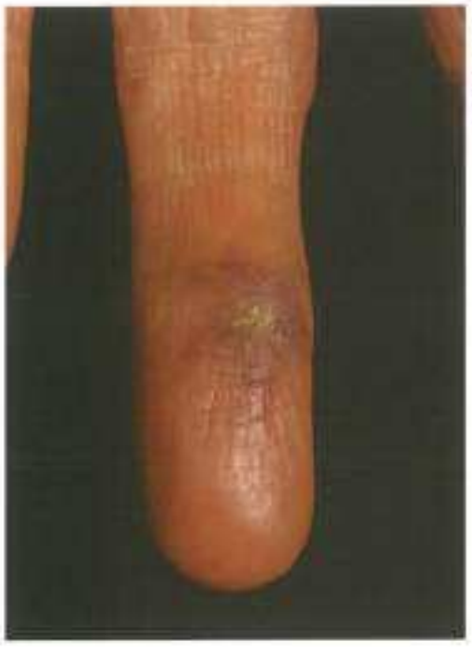


Fig. 9.151 Glomus tumour. A red nodule is present on the finger, a typical site. (Courtesy of the Institute of Dermatology.)

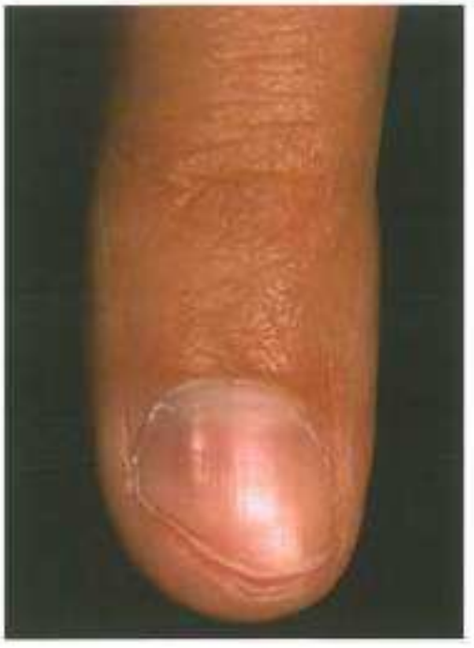


Fig. 9.152 Glomus tumour. A red papule is present under the nail. Typically it is paroxysmally painful, often precipitated by cold or pressure.

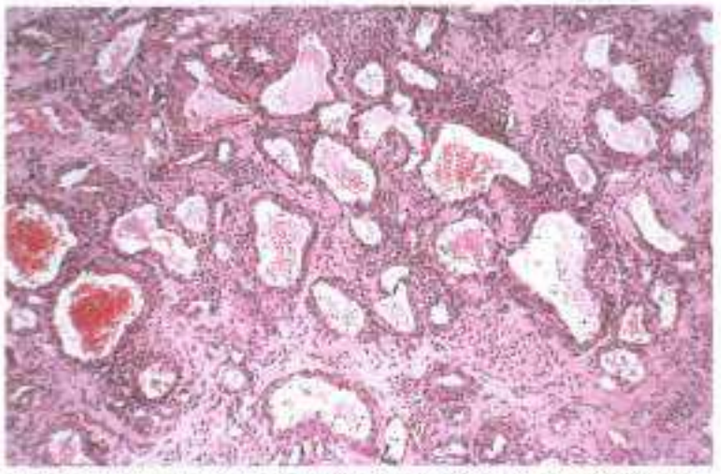


Fig. 9.153 Glomus tumour. Low-power view showing dilated vascular channels surrounded by a mantle of small eosinophilic cells.

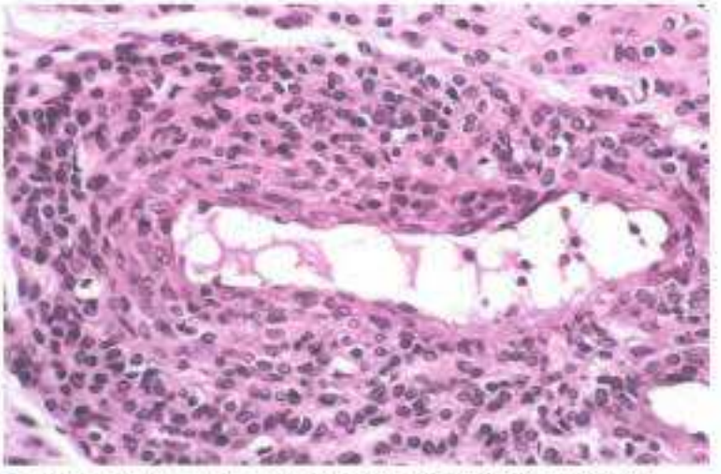


Fig. 9.154 Glomus tumour. The endothelial-lined vessel is surrounded by a broad sheath of regular 'glomus' cells with uniform nuclei and indistinct cytoplasmic margins.

GLOMUS TUMOUR

An episodically painful tumour of modified smooth muscle cells in the Sucquet–Hoyer canal.

Clinical Features

Symptoms

Paroxysmal pain, is often precipitated by cold, pressure or dependency.

Morphology

A small flesh-coloured or red papule or nodule (Fig. 9.151).

Distribution

Glomus tumours are usually seen on the hands, particularly the palms and beneath the nails (Fig. 9.152), although they may occur anywhere.

Histopathology

It is a benign vascular neoplasm that arises from the glomus cells of the Sucquet–Hoyer canal, which is involved in temperature regulation in acral sites. It is an arteriovenous coiled shunt composed of arterial and venous segments united by a vascular channel, the media of which contains cuboidal modified smooth muscle cells.

The solitary glomus tumour is composed of dilated blood-filled vascular channels lined in part by endothelial cells but also by cuboidal cells with eosinophilic cytoplasm (glomus cells) (Fig. 9.153). The latter component is often multilayered. In many areas, the wall of the vessel contains large numbers of glomus cells (Fig. 9.154). Glomus tumours are richly innervated. The lesions from patients with multiple glomus tumours are characterized by larger vascular channels with much less conspicuous glomus cells.

Management

Diagnosis of a glomus tumour is not usually difficult, because of the pain. Multiple lesions inherited as an autosomal dominant do occur in childhood. Glomus tumours must be excised completely, otherwise recurrence is frequent.

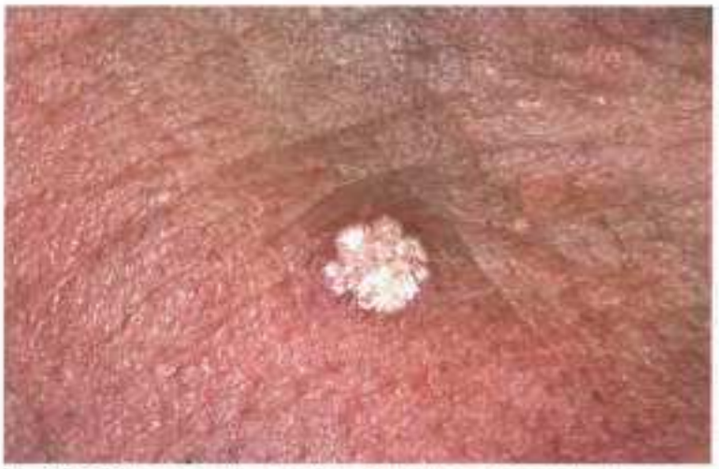


Fig. 9.155 Calcinosis cutis. A solitary white hard papule or nodule may occur without any obvious explanation.

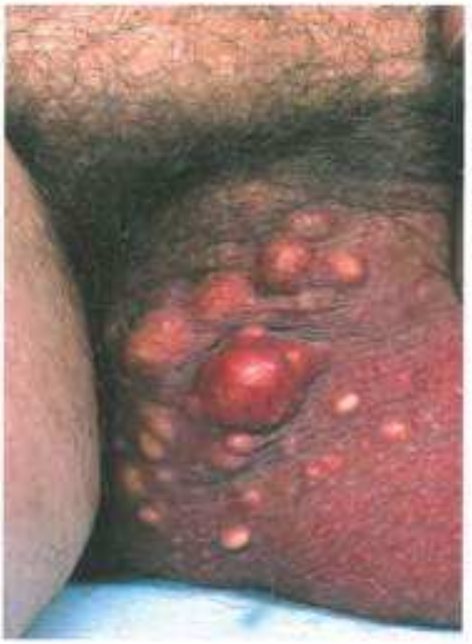


Fig. 9.156 Idiopathic calcified nodules of the scrotum. There are multiple firm papules or nodules on the scrotum. They possibly represent calcified epidermoid cysts. A similar condition may occur on the vulva. They may be excised.

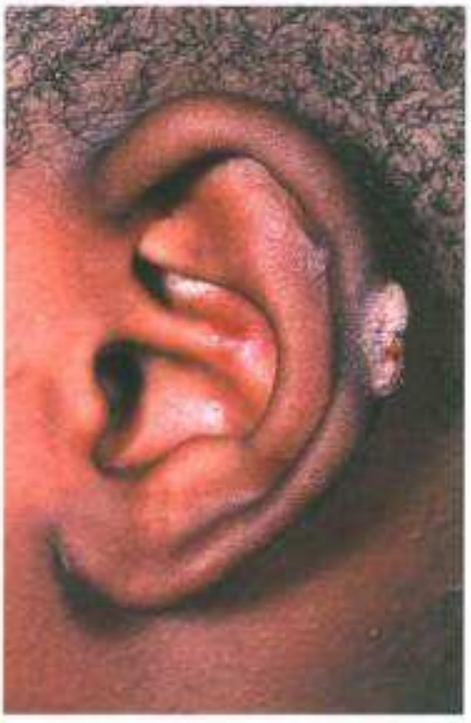


Fig. 9.157 Solitary nodular congenital calcification. This is a characteristic lesion on the ear of an infant. The cause is unknown, but it may be due to trauma in utero.

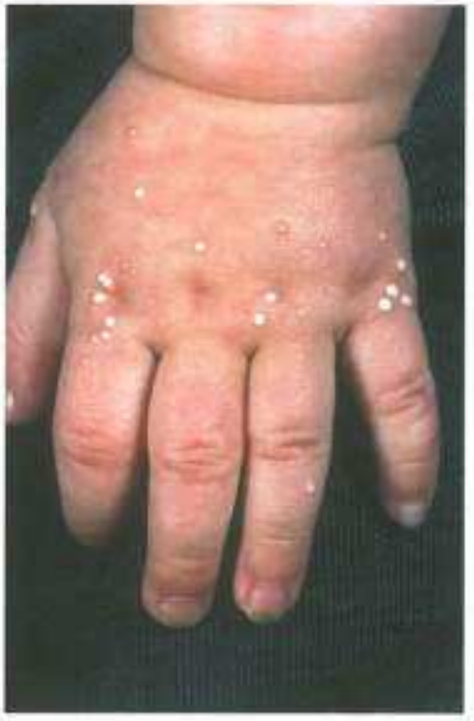


Fig. 9.158 Milia-like calcinosis. Multiple small white papules on the backs of the hands and fingers are a striking condition. Although they look like milia they contain calcium and occur particularly in Down's syndrome.

CALCINOSIS CUTIS

Calcification may occur in the skin:

- in certain autoimmune disorders (CREST and dermatomyositis)
- in pancreatic panniculitis
- in genetic disorders (pseudoxanthoma elasticum, Ehlers–Danlos syndrome, chronic sclerodermoid porphyria cutanea tarda, Werner's and Rothmund–Thomson syndrome) or part of specific disorders involving cutaneous ossification such as Albright's syndrome
- after infections, particularly calcified parasitic cysts (onchocerciasis and taenia solium) and following intrauterine herpes simplex
- in certain neoplasms, e.g. pilomatrixoma and pilar cysts
- following trauma (heel stick blood sampling in infants) or extravasation of calcium gluconate or chloride infusions
- as metastatic calcification in renal disease, hypervitaminosis D or the milk alkali syndrome
- as an idiopathic phenomenon (Fig. 9.155)
- in the scrotum (Fig. 9.156),
- on the head and neck, especially ears (Fig. 9.157) in children (syn. *solitary nodular congenital calcification of Winer*)
- as milia-like small lesions on the backs of the hands (Fig. 9.158) and face often associated with Down's syndrome (*milia-like calcinosis*)
- as a miliary-like phenomenon on the cheeks, either spontaneously or secondary to acne.

Dental abscess

Although clearly not a skin tumour, it is frequently misdiagnosed as such. It presents on the cheek or jaw (Figs 9.159 and 9.160) and results from a periapical tooth abscess causing a sinus which leads to the skin. A stitch abscess (Fig. 9.161) may also produce a fleshy papule but the preceding surgery makes the diagnosis obvious.

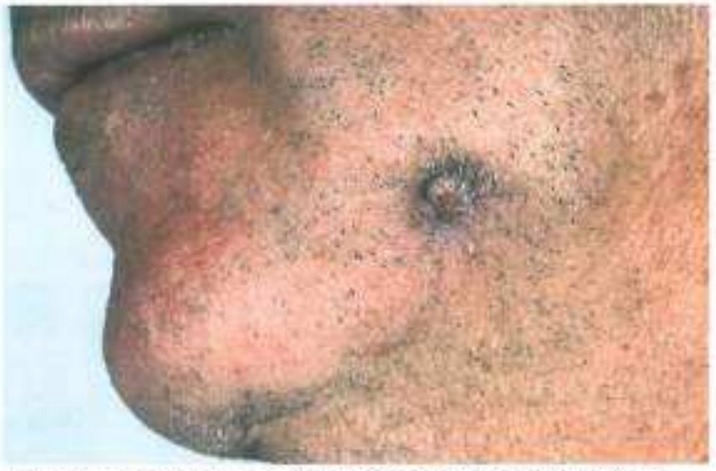


Fig. 9.159 Dental abscess. There is a fleshy papule over the jaw. It results from a periapical abscess, which causes a sinus if untreated and drains out onto the skin.

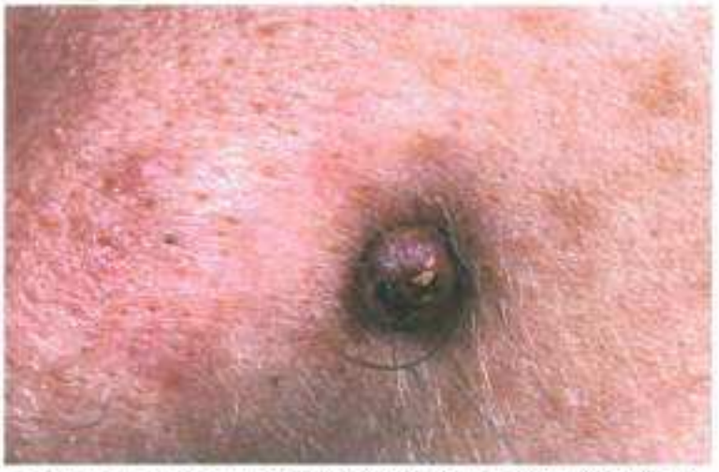


Fig. 9.160 Dental abscess. The fleshy red papule with surrounding indentation does not respond to surgery (it just recurs). An orthopantomograph will demonstrate the abscess. It responds to treatment of the tooth and its abscess.

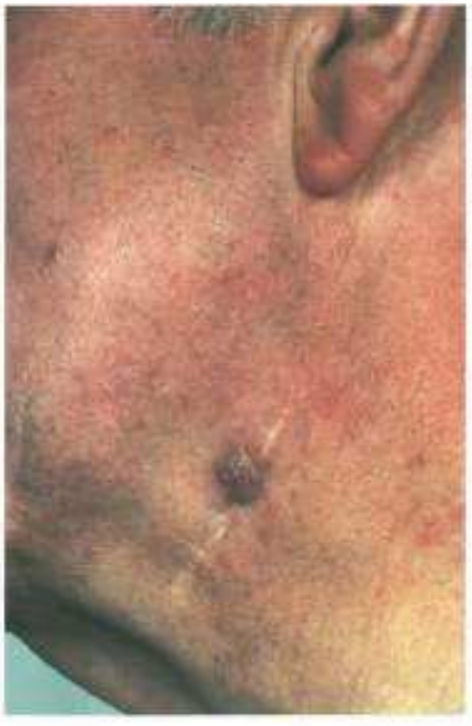


Fig. 9.161 Stitch abscess. The surgical scar is obvious and the nodule could easily be misdiagnosed as a recurrence of the tumour but it was due to a residual stitch.

Non-melanoma skin cancer 10

Solar damage and skin cancer

The prevalence of skin cancer is increasing as a result of cumulative or intense exposure to solar irradiation. Although it is more common in white North Americans, South Africans and Australians, it is a British or Northern European disease because it is their cutaneous phenotype that makes them prone to it.

The problem is compounded by the dictates of fashion, the ease of access to the sun, the hole in the ozone layer and the increasing longevity of the population. Even if effective solar protection becomes the norm, there is nothing that can be done to reverse damage already done; consequently, the problem is likely to be with us well into the 21st century.

The propensity for solar damage depends upon:

- the patient's skin type
- the cumulative exposure to ultraviolet light
- the intensity of exposure
- the exposure in childhood
- residence nearer to the equator.

Skin types reflect vulnerability to skin cancer and may be classified as:

1. Always burns, never tans
2. Always burns, sometimes tans
3. Sometimes burns, always tans
4. Never burns, always tans
5. Black skin.

Types 1 and 2 are most susceptible. Ultraviolet-induced skin cancer does not occur in black (type 5) skin. The red-headed, blue-eyed, fair-skinned individual who burns and freckles easily is most at risk, but appearances are deceptive. Therefore, although dark-haired, brown-eyed and olive-skinned people are usually better protected, it is their response to sunlight that matters. If they burn, their skin type may be 1 or 2; therefore, they will be in a high-risk group.

The amount of exposure is important. The link between sunlight and skin cancer was first established in sailors who travelled around the world. Solar keratoses and squamous cell carcinomas occur as a result of chronic exposure and are most common in those who spend a lot of time outdoors and become chronically weather beaten.

The intensity of exposure is also relevant. For example, certain forms of malignant melanoma are most common in workers who are ensconced in their offices or factories most of the year and who expose their white, non-tanned skin intensely on vacation, often burning in the process.

The timing of exposure is important. Much of the damage may be done in childhood. Therefore, indigenous Australians are more prone to malignant melanoma than Europeans who emigrate to Australia in their teens. Indeed it is an important part of the management of the problem to advise patients who have skin cancer of the potential danger to their children and grandchildren through having inherited a similar skin type. The proximity to the equator is relevant. Those living in southern California are at greater risk of skin cancer than those in northern California; those living in Queensland, Australia have the highest incidence of malignant melanoma in the world and yet this decreases with increasing distance from the equator in Australia. Non-melanoma skin cancer is four times more common in northern as opposed to southern Australia.

Ultraviolet light is classed as UVC (200–280 nm), UVB (280–315 nm) and UVA (315–400 nm). The ozone layer blocks all ultraviolet light below 290 nm, which includes a substantial proportion of UVB band; however, there has been a decrease in the ozone layer in recent years. Only UVA reaches the dermis. The rest is absorbed by the epidermis. Ultraviolet light causes direct tissue and cellular damage. It causes local and systemic immunosuppression, as evidenced by decreased numbers of Langerhans' cells, reduced delayed hypersensitivity reaction to known allergens and enhanced susceptibility to transplanted tumour cells. Skin cancer is increased in the immunosuppressed and is more aggressive. The consequences of ultraviolet irradiation are photoageing, mutations and carcinogenesis.

p53 (regarded as the guardian of the genome) is an anti-oncogene located on chromosome 17p and encodes for a large protein that prevents cells from entering S-phase until DNA repair enzymes can excise abnormal nucleotides; this prevents mutations being passed on to daughter cells. If DNA damage occurs too far along the cell cycle, p53 can still play a crucial role by activating genes that can cause programmed cell death (apoptosis). This function is lost in 50% of human tumours and, as a result, replication occurs with reduced fidelity and leads to cell transformations and cancer. Mutations are found in p53 tumour suppressor genes in squamous cell carcinoma. Mutations affecting p53 are, therefore, characteristic of sun damage.

Other skin cancers are described in this chapter that are not caused by solar irradiation. These include Merkel cell tumour, microcystic adnexal carcinoma, sebaceous carcinoma, dermatofibrosarcoma protuberans, cutaneous angiosarcoma and Kaposi's sarcoma.

Physical Signs of Solar Damage

Sunburn (Fig. 10.1) is the first acute sign of solar damage in childhood. It is caused by UVB and results in painful erythema and sometimes oedema and blistering. It is followed by desquamation (peeling). It is preventable

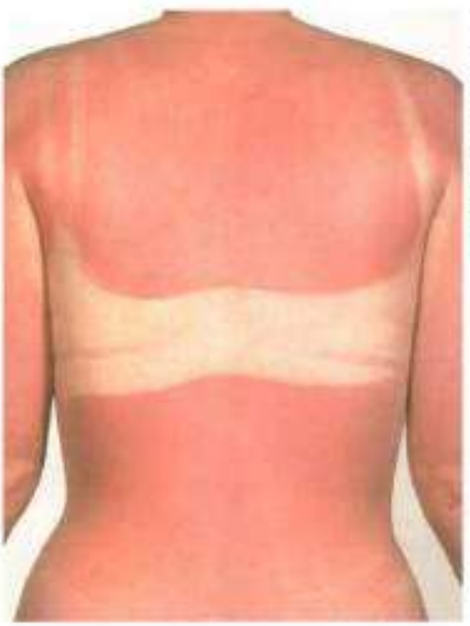


Fig. 10.1 Sunburn. Erythema is induced by ultraviolet B but is preventable with sunscreens and protective clothing. Sunburn is ultimately responsible for premature ageing of the skin and many skin cancers.

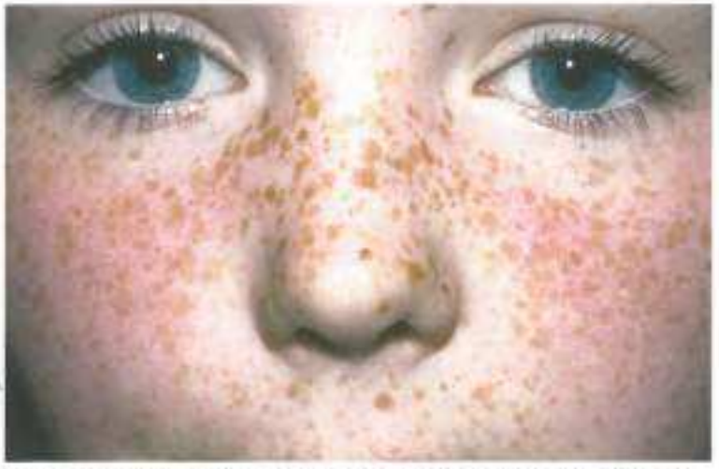


Fig. 10.2 Freckles. Freckles appear in the summer and fade in the winter. They indicate that damage is occurring in the skin. Advice regarding solar protection is very important at this age.

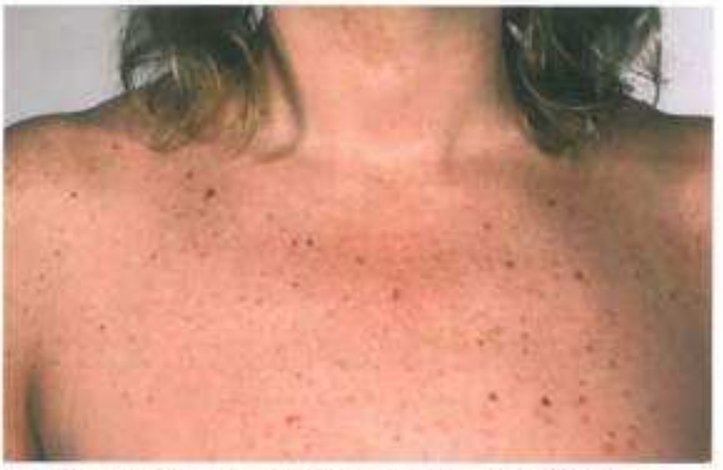


Fig. 10.3 Solar lentigines. These permanent, even-coloured macules or patches indicate sun damage and photoageing often acquired in a sunny climate in childhood. She was in her twenties.

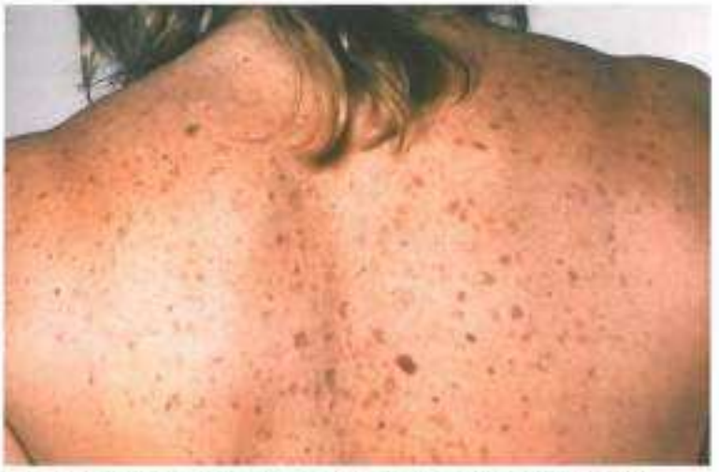


Fig. 10.4 Solar lentigines and seborrhoeic warts. These liver-coloured macules and patches result from childhood sun exposure. The slightly darker lesion is a seborrhoeic wart.

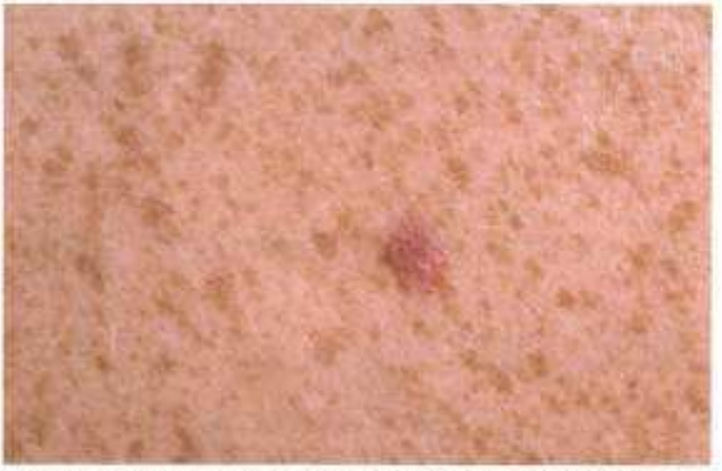


Fig. 10.5 Solar lentigines and a basal cell carcinoma. There are many flat evenly pigmented liver-coloured macules in this 25 year old, indicating chronically sun-exposed skin with a basal cell carcinoma in the centre.

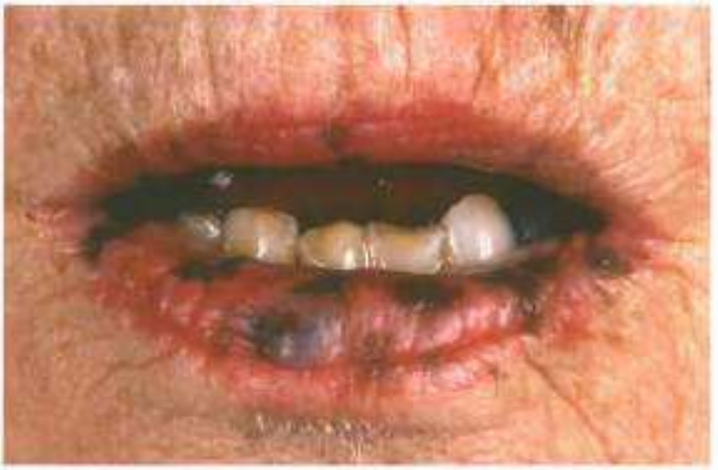
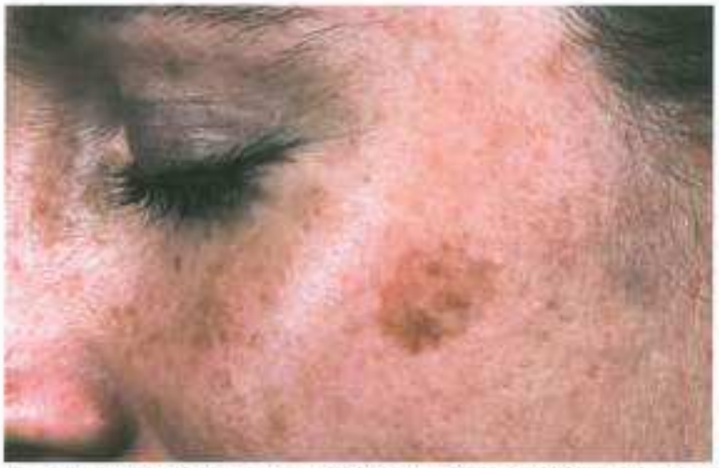


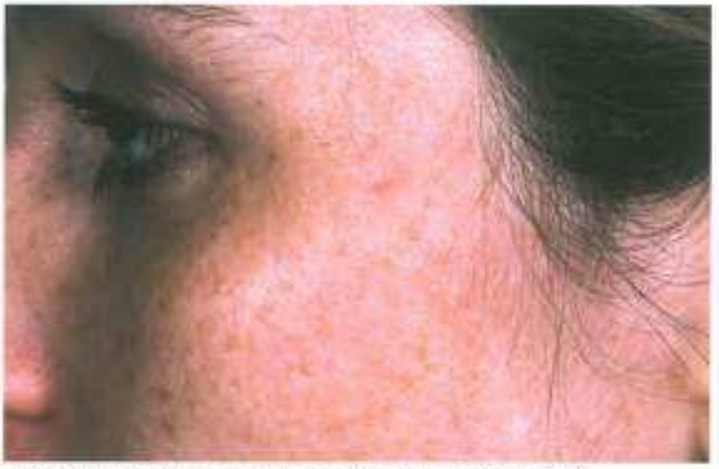
Fig. 10.6 Solar lentigines. They may occur on the lips, especially the lower. Note the furrowing of the skin from chronic damage.

with sunscreens. Subsequently, sunburn is followed by freckles in Type 1 and 2 skins. The action spectrum of erythema is similar to the absorption spectrum of DNA and there is evidence for close links between erythema (sunburn) and DNA damage. Pyrimidine bases are very sensitive to sunlight. Dimers and photoproducts are formed from adjacent base pairs and these have to be excised to prevent mutations. Sunburn cells (keratinocytes that contain DNA which is too damaged to be repaired) are an indication of p53-induced apoptosis and are noted in quite significant numbers even with suberythema doses. Sunburn begins 4 hours after exposure and peaks between 8 and 24 hours. Repeated sunburn is an independent risk factor for both malignant melanoma and non-melanoma skin cancer.

Chronic solar exposure results in *dermatoheliosis*, a state of wrinkling, mottled pigmentation, coarseness, telangiectasia, laxity and atrophy of the skin later in life (photoageing). All these changes can be seen in an accelerated form in the rare disorder *xeroderma pigmentosum*, a condition of extreme photosensitivity that results from an enzymatic failure to repair ultraviolet light-damaged epidermal DNA. In this condition, multiple types of skin cancer begin in childhood.

Freckles are ultraviolet-induced increases in melanin production without melanocytic proliferation, which diminish in winter, occurring





Figs 10.7 and 10.8 Solar lentigo. The lesion is a light yellow and brown patch. It was treated with liquid nitrogen and was still clear 2 years later (Fig. 10.8).

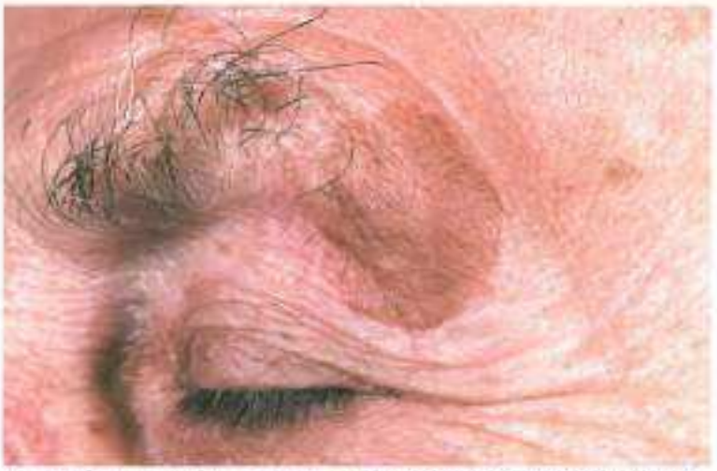


Fig. 10.9 Seborrhoeic wart. This liver-coloured lesion is well defined and barely raised and represents a solar lentigo evolving into a seborrhoeic wart.

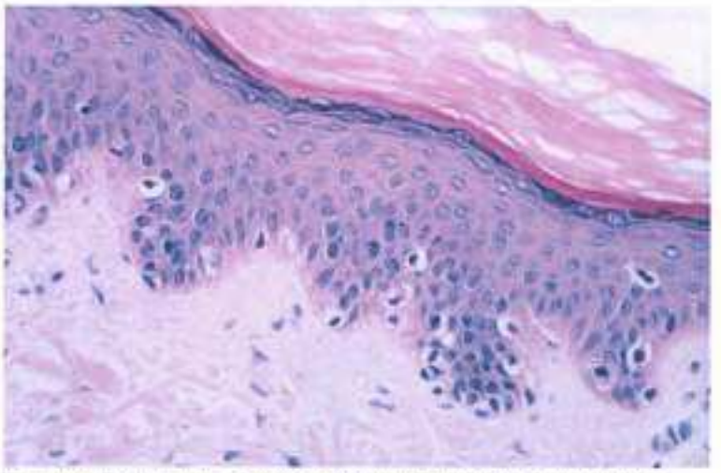


Fig. 10.10 Solar lentigo. There is hyperkeratosis. The rete ridges are slightly elongated. There are increased numbers of basally located melanocytes, but no junctional activity.

in children with type 1 and type 2 skins, predominantly on the face, especially the cheeks and nose (Fig. 10.2).

Solar lentigines (often known as 'liver' or 'age' spots) are even-coloured macules or patches that vary from light tan to dark brown in colour (Fig. 10.3), occurring on sun-exposed areas, particularly the face, lips, backs of the hands, extensor surfaces of the arms, front of the chest, upper back (Figs 10.4 and 10.5) and shoulders. The lips may be involved (Fig. 10.6). They may occur singly (Figs 10.7 and 10.8) or in profusion. Although lesions are usually quite flat, they may be just slightly raised with a matt appearance simulating a seborrhoeic wart (Fig. 10.9). Histologically there is hyperkeratosis. The rete ridges of the epidermis are slightly elongated and there are increased numbers of benign basally located melanocytes. There is no junctional activity (Fig. 10.10). There is usually evidence of solar elastosis in a solar lentigo but not in a simple lentigo which is not sun related and may be associated in increased numbers with various cardiac, endocrine or the Peutz–Jegher syndromes.

Gradually solar damage occurs to the elastic fibres in the dermis, producing microscopically a rather dramatic picture of disarray known as *solar elastosis* (Fig. 10.11). Clinically a number of appearances may result.

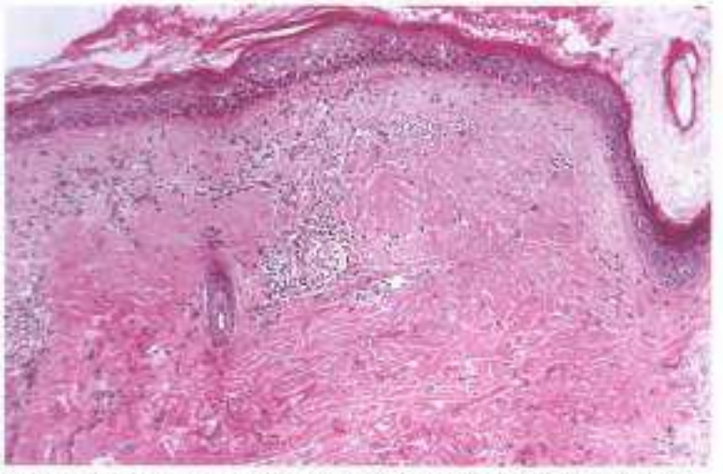


Fig. 10.11 Solar elastosis. There is diffuse homogenization of the connective tissue and a focal chronic inflammatory infiltrate in the upper reticular dermis below a solar keratosis.

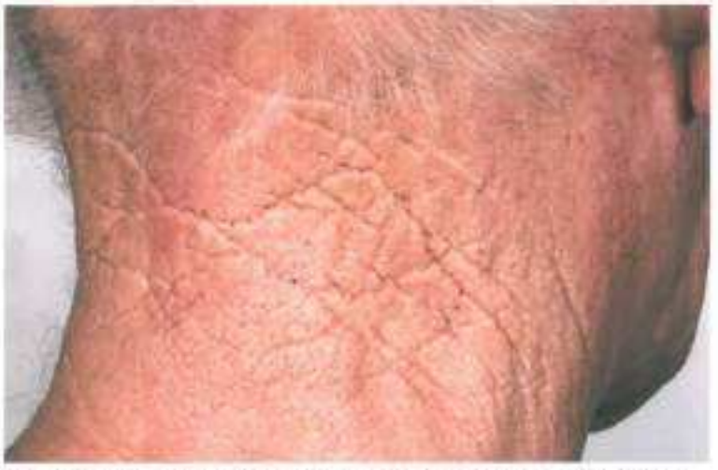


Fig. 10.12 Cutis rhomboidalis nuchae. The skin is yellow and furrowed with many comedones and contrasts with the undamaged skin lower down the neck, which has been protected by the shirt collar.

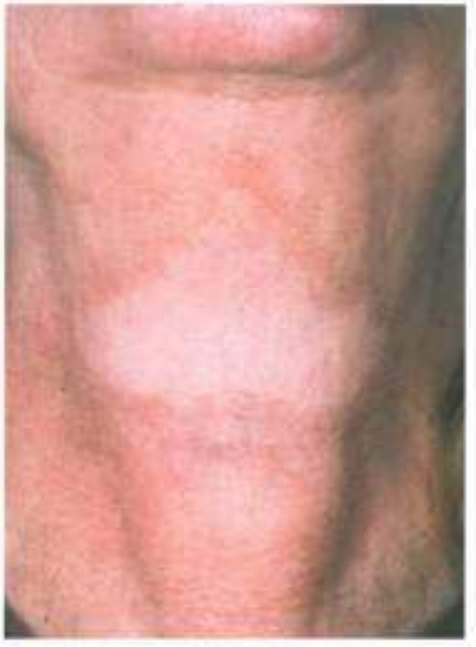


Fig. 10.13 Photo-ageing. The area on the neck which is protected from solar irradiation by the jaw is unblemished in this 69-year-old Caucasian.

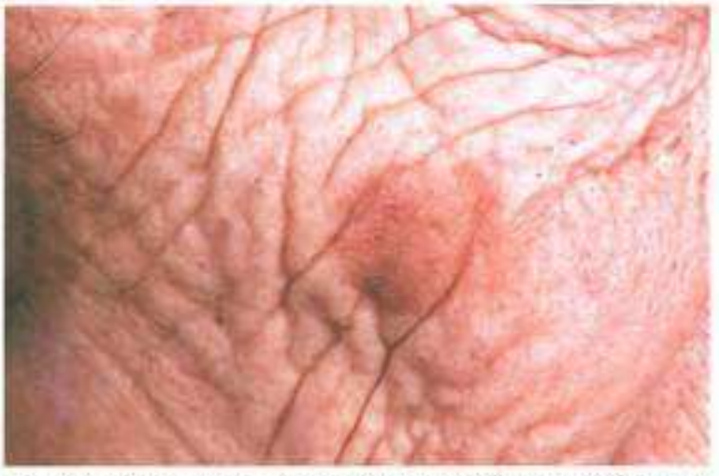


Fig. 10.14 Wrinkles with a seborrhoeic wart. The skin is yellow, thickened and lined due to solar elastosis. A seborrhoeic wart is present in the centre of the photograph.

- **Cutis rhomboidalis nuchae** The skin is thrown into exaggerated coarse folds, particularly around the neck (Fig. 10.12), but with impressive sparing of the sun-shielded area under the chin (Fig. 10.13).
- **Wrinkles** These occur as a result of solar elastosis and there is also evidence that smoking acts synergistically to increase them (Fig. 10.14).
- **Atrophy of the skin** The skin loses its elasticity, particularly on the dorsal aspects of the hands, forearms and shins. It is dry, wrinkled and thin (Fig. 10.15). The blood vessels are vulnerable and purpura results from the slightest trauma (Fig. 10.16).

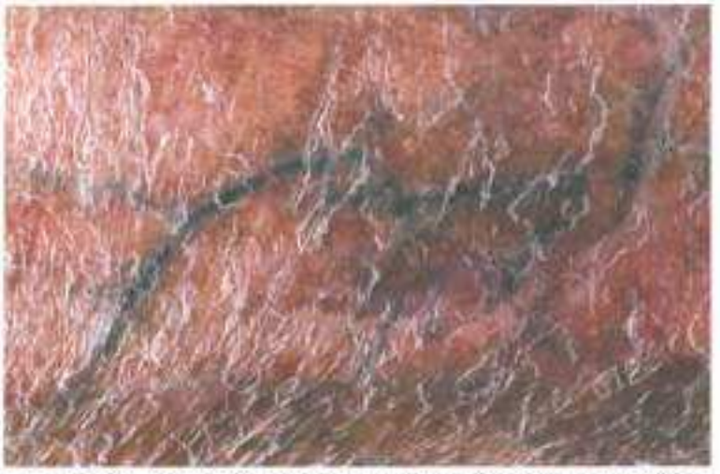


Fig. 10.15 Solar atrophy. Skin on the back of the hands is especially vulnerable. It loses its elasticity, is dry, wrinkled and thin. The underlying vasculature is obvious.

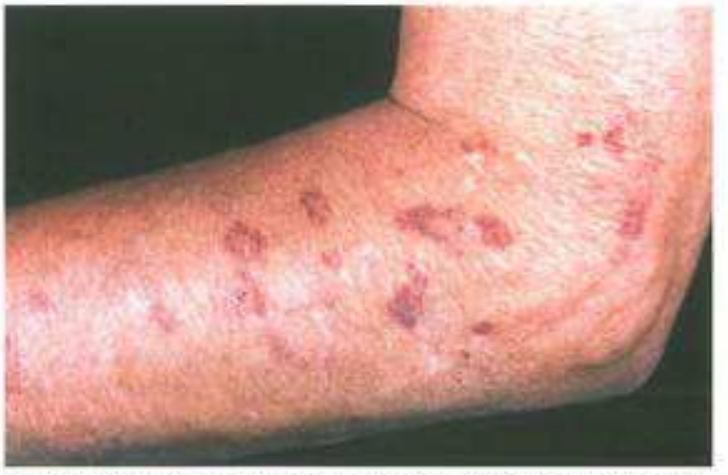


Fig. 10.16 Solar purpura. There are many purpuric patches in this octogenarian. The forearms and backs of the hands are the common sites. A similar appearance occurs in steroid induced purpura.

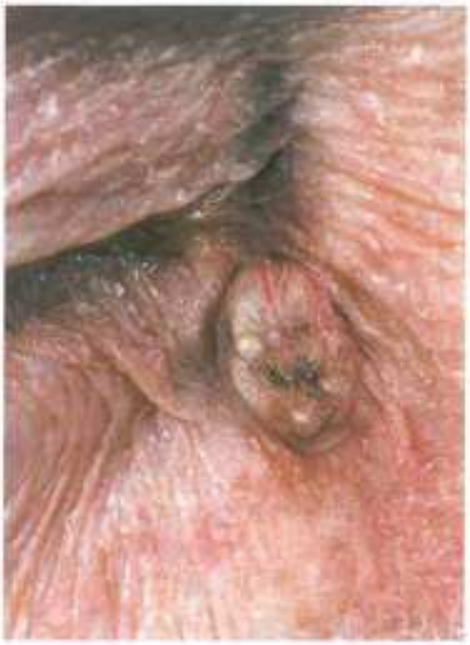


Fig. 10.17 Senile milia. These solitary lesions in the elderly, particularly around the eye, may be mistaken for xanthelasma or a basal cell carcinoma. This lobulated white lesion often plugged with comedones is common in photoageing.

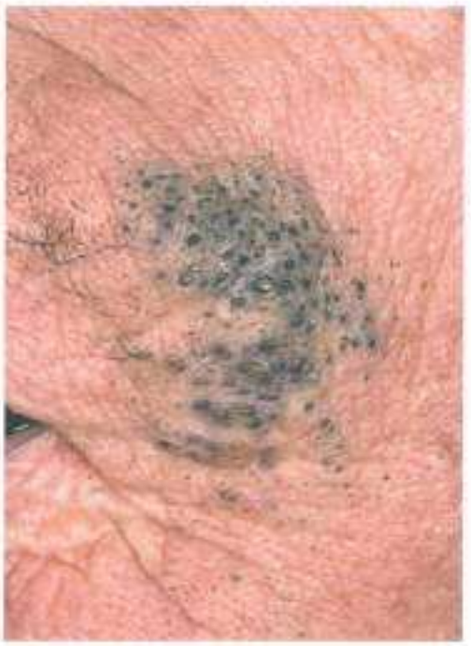


Fig. 10.18 Favre–Racouchot syndrome. Multiple comedones are present with solar elastosis and often milia. This is extreme photoageing which is often compounded by cigarette smoking.

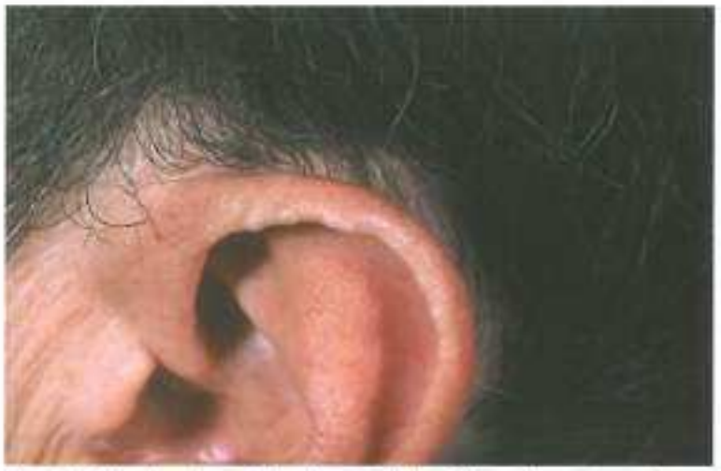


Fig. 10.19 Weathering nodules. The outer helix of the ear is prone to solar damage in males. The collagen becomes damaged and small firm white papules occur at the rim of the helix.

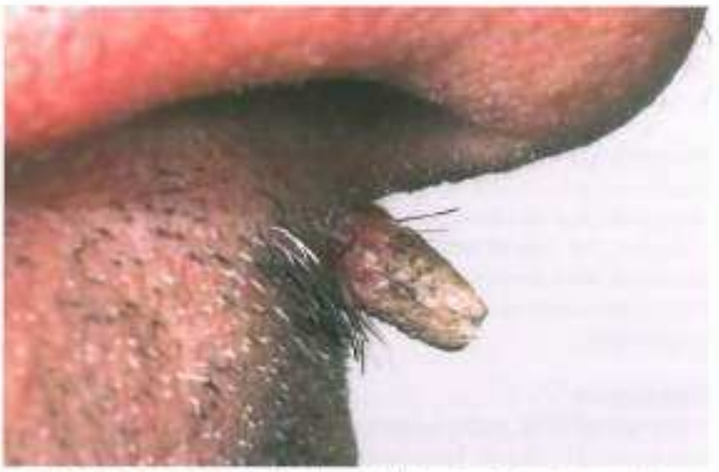


Fig. 10.20 Cutaneous horn. There is marked keratin adhesion that results in a horny outgrowth, in this lesion resulting from a small keratoacanthoma. Other causes include warts, actinic keratoses and squamous cell carcinoma.

- **Comedones, milia and yellow plaques** Blackheads, whiteheads (Fig. 10.17) and yellow plaques are common features of chronically sun-damaged skin. Comedones are thin-walled epidermoid cysts in the upper dermis associated with marked solar elastosis. The malar region and around the orbits are particularly affected (Fig. 10.18). Extreme examples are sometimes known as the *Favre–Racouchot syndrome* (nodular elastoidosis).
- **Weathering nodules of the ears** Small white firm papules (Fig. 10.19) result from damage to the collagen on the outer helix in males with short hair.
- **A cutaneous horn** is a descriptive term for marked keratin cohesion that gives rise to a horny outgrowth (Figs 10.20 and 10.21). It may be caused by a wart (viral or seborrhoeic), solar keratosis, keratoacanthoma or squamous cell carcinoma. Examination of the base of the lesion may be helpful. A flat or very slightly raised red base suggests a keratosis; a well-defined warty base, a seborrhoeic wart; and a red indurated base, a squamous cell carcinoma. Surgical removal and histological examination is the treatment of choice.

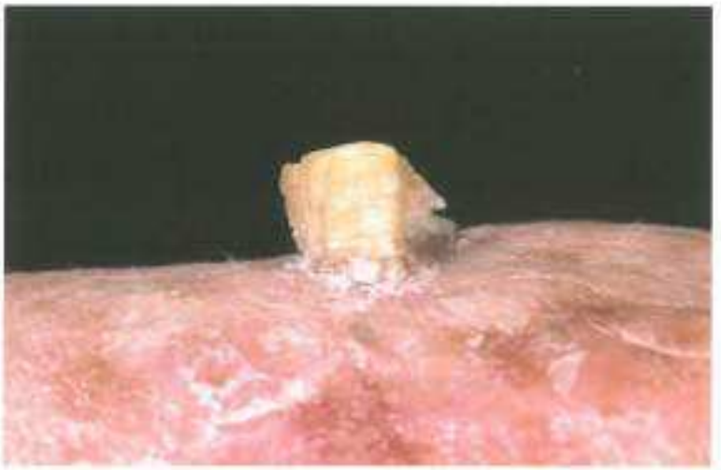


Fig. 10.21 Cutaneous horn. There is marked keratin adhesion that results in a horny outgrowth, in this lesion resulting from an actinic keratosis. Other causes include warts, keratoacanthoma and squamous cell carcinoma.

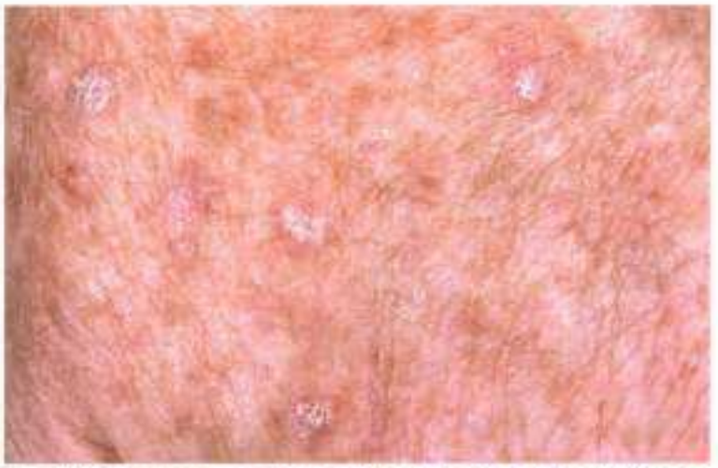


Fig. 10.22 Solar keratoses. There are pink papules with a rough adherent scale occuring on sun-damaged exposed skin.

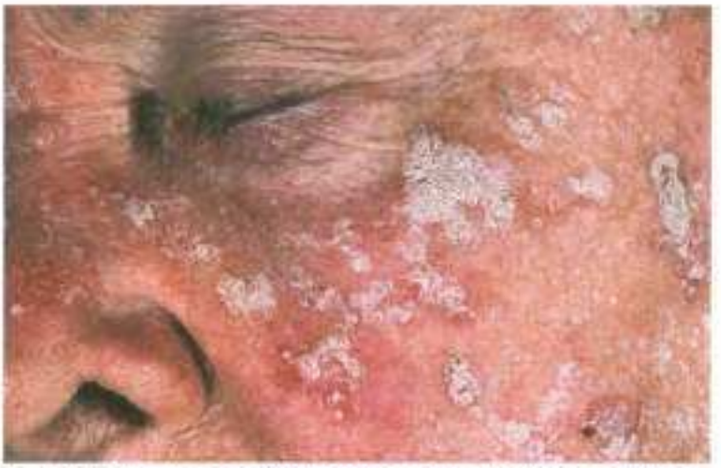


Fig. 10.23 Solar keratoses. Multiple lesions are frequent especially on the face in patients with a type 1 skin. Celtic races are particularly at risk.

Solar keratosis

A premalignant epidermal disorder occurring on solar-damaged skin.

Clinical Features

Symptoms

Rough, sometimes sore spots.

Morphology

It starts as a minute area of telangiectasia and proceeds to a well-defined, red papule (Fig. 10.22) or plaque, with a rough, adherent, yellow-brown scale that can only be removed with difficulty, leaving a raw bleeding surface. A solar keratosis is potentially malignant and may gradually become thickened, resulting in squamous cell carcinoma. However it rarely metastasizes.

Distribution

Often multiple (Fig. 10.23) on chronically solar-exposed skin, i.e. the face, ears, backs of the hands, forearms and shins. The scalp of a man who has been bald from youth is particularly vulnerable (Fig. 10.24) and liable to form solar keratoses (often misdiagnosed as eczema).

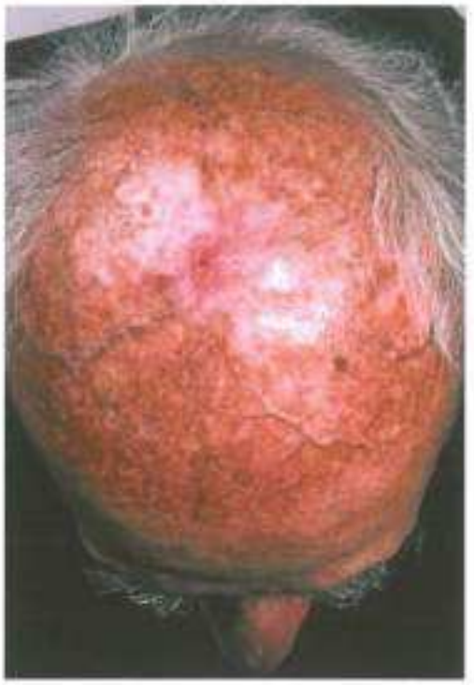


Fig. 10.24 Solar damage and squamous cell carcinoma. Hair is photoprotective. Men who go bald at an early stage and who do not wear a hat are prone to solar keratoses and squamous cell carcinomas (centre of field). There is gross atrophy and the patient is suntanned.

Histopathology

Solar keratoses are characterized by variable degrees of dysplasia, ranging from mild changes through to carcinoma in situ.

The most frequent type is composed of variably acanthotic squamous epithelium covered by a thickened scale of alternating parakeratotic and hyperkeratotic horn. The parakeratosis overlies the dysplastic epidermis and the hyperkeratosis is related to uninvolved intraepidermal adnexal structures. The epidermis frequently buds down into the underlying dermis. Epithelial dysplasia is constant and consists of loss of maturation, abnormalities of cellular polarity, nuclear and cytoplasmic pleomorphism, individual cell keratinization and abnormally located (and often abnormally structured) mitotic figures. In contrast to Bowen's disease, the dysplasia tends not to involve the intraepidermal components of the adnexal structures, but it may surround the latter to give a 'mantle-like' effect (Fig. 10.25). Elastosis is a frequent manifestation in all solar keratoses.

The atrophic type is characterized by hyperkeratosis and parakeratosis, which overlies a thinned epidermis, and shows predominantly basal and suprabasal epithelial dysplasia (Fig. 10.26). Bowenoid solar keratoses show full thickness dysplasia and are histologically indistinguishable from Bowen's disease. The acantholytic solar keratosis, in addition to epithelial dysplasia, is typified by suprabasal cleft formation.

A *lichenoid keratosis* is an uncommon, usually solitary, lesion (Fig. 10.27 and Fig. 7.71) with a histology that is very similar to that of lichen planus, although there may be focal areas of parakeratosis and a degree of epithelial dysplasia, which will sometimes serve to distinguish the two; the clinical context should permit the differential diagnosis.

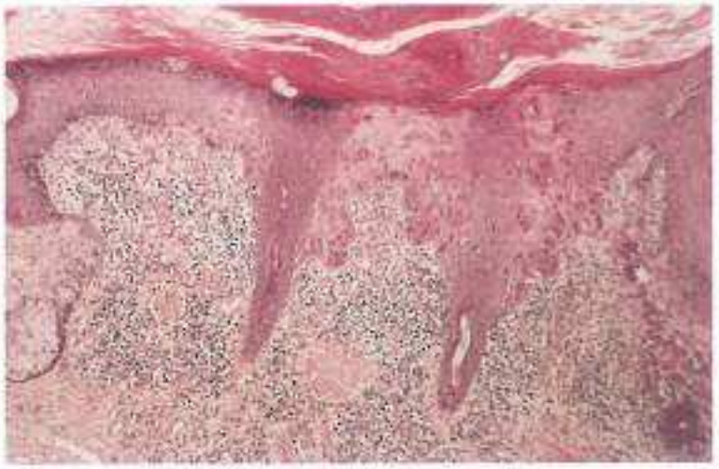


Fig. 10.25 Solar keratosis. On the left is relatively normal squamous epithelium. On the right is focal epidermal dysplasia involving the basal layers. The uninvolved epidermis shows hyperkeratosis, the involved parakeratosis.

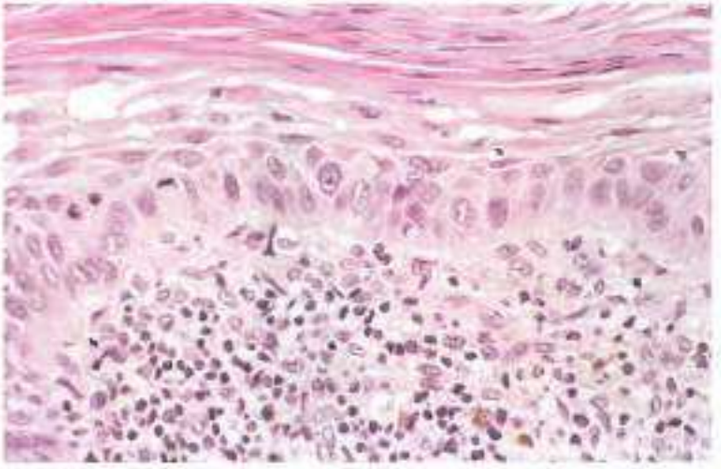


Fig. 10.26 Atrophic solar keratosis. There is parakeratosis. Dysplastic features (nuclear pleomorphism and mitotic activity) are present in the lower epidermis. Intense chronic inflammation is present in the upper dermis.

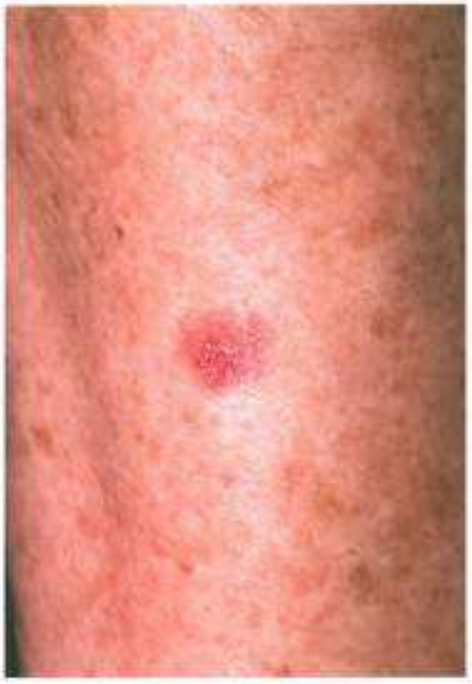


Fig. 10.27 Lichenoid keratosis. There is a red plaque occurring on sun-damaged skin. It may be difficult to diagnose clinically but the histology is similar to lichen planus.

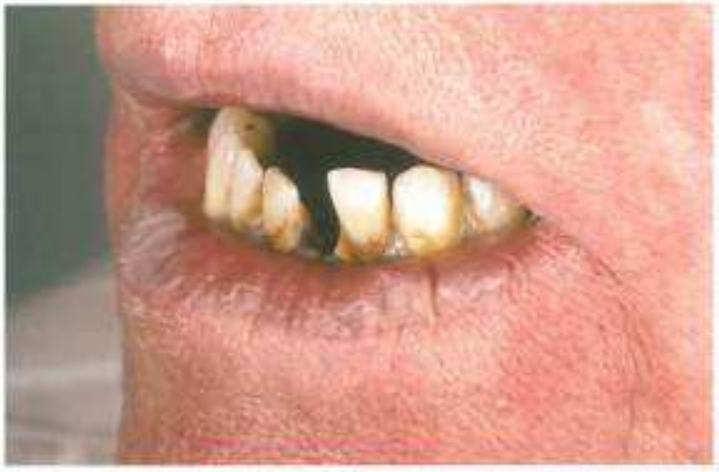


Fig. 10.28 Actinic cheilitis. The lower lips are vulnerable to solar irradiation. Well-defined premalignant white patches may result.

Actinic cheilitis

A premalignant change affecting predominantly the lower lip.

Clinical Features

Symptoms

There is a dryness and scaling of the lower (more protruberant than the upper) lip, which may split and crust and proceed to white patches (Fig. 10.28).

Morphology

Dry, whitish patches or plaques with fissuring.

Distribution

The lower lip.

Histopathology

The features of actinic cheilitis range from epidermal dysplasia to carcinoma in situ. There is a greater risk of transformation to squamous cell carcinoma in actinic cheilitis than in actinic keratoses. Squamous cell carcinoma is also associated with a greater risk of metastases. Leukoplakia is an outdated term previously used to describe the condition but this simply means a white plaque, which gives no indication of the pathology and could easily describe a totally benign condition such as lichen planus of the lips.

Disseminated superficial actinic porokeratosis

A distinctive eruption of well-defined, small annular lesions with a keratotic rim, occurring principally on the legs.

Aetiology

Although believed to be actinic in origin, it is not that common and other factors including immunosuppression (either drug induced following organ transplantation or from a malignancy such as chronic lymphatic leukaemia) or familial may be relevant.

Clinical Features

Symptoms

Asymptomatic disfiguring patches on the limbs.

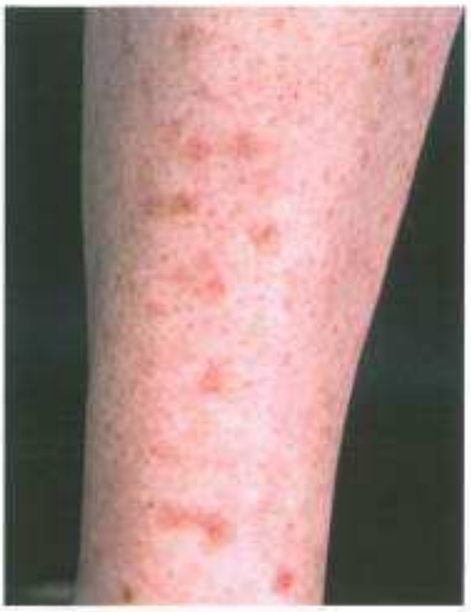


Fig. 10.29 Disseminated superficial actinic porokeratosis. The lesions have a well-defined, slightly raised, keratotic margin with an atrophic red centre.

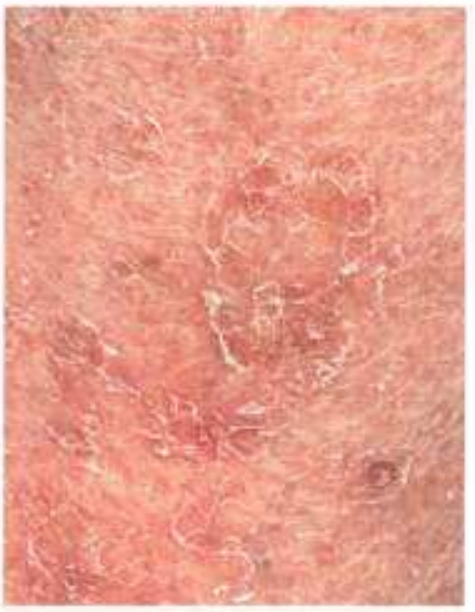


Fig. 10.30 Disseminated superficial actinic porokeratosis. Multiple lesions occur on the limbs. Actinic damage or immunosuppression may cause it. (Courtesy of St Mary's Hospital.)

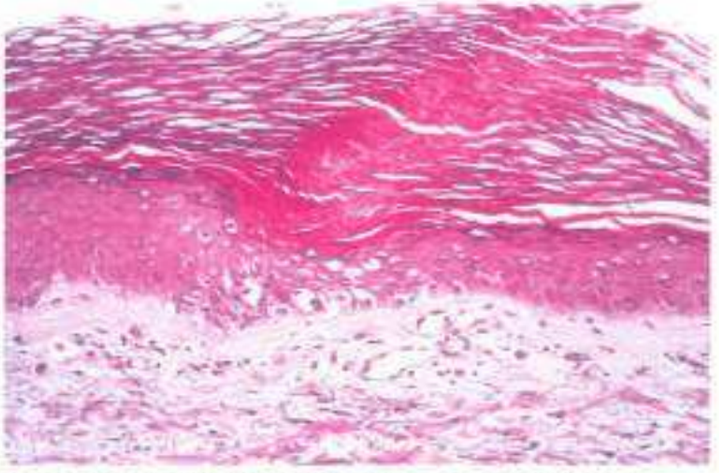


Fig. 10.31 Disseminated superficial actinic porokeratosis. There is a cornoid lamella, absence of the granular cell layer and conspicuous cytoplasmic vacuolation at the base of the tier. (Courtesy of the late Dr Neil Smith.)

Morphology
Multiple (Fig. 10.29) plaques with a very well-defined, slightly raised keratotic margin and a somewhat atrophic red centre (Fig. 10.30).

Distribution
Multiple, usually present on the shins and sometimes the arms.

Histopathology
Fundamental to the process of porokeratosis is the formation of the cornoid lamella. This consists of an angulated tier of keratin that is orientated at an obtuse angle to the epidermis. At its lower border, the epithelium is vacuolated, while at the edges there is a well-formed granular cell layer (Fig. 10.31). Towards the centre of the lesion, the epithelium is often atrophic.

Management
There is no particularly effective treatment, although cryotherapy, 5-fluorouracil and retinoic acid are often used. Sometimes actinic keratoses or Bowen's disease are also present.

Bowen's disease
An intraepidermal carcinoma of the skin that occasionally proceeds to squamous cell carcinoma.

Aetiology
It is relatively common. The majority result from chronic ultraviolet light irradiation of exposed skin. However, arsenic ingestion should be suspected in patients with multiple lesions on covered sites. Only 5% recall arsenic ingestion, but statistically significant quantities of arsenic may be found in their skins. Arsenic has been used therapeutically as Fowler's solution for psoriasis and syphilis, in combination with bromide for epilepsy and chorea, and in Gay's solution as a treatment for asthma in the USA. It is used industrially as a weed killer, pesticide, sheep dip and fungicide. It was formerly incorporated in many children's tonics, including Parrish's food, in many homeopathic preparations and in American tobacco. Arsenic may also predispose to internal malignancy and multiple superficial basal cell carcinomas of the skin.

The role of human papilloma virus (HPV) is well established in genital Bowen's disease but it is not so clearly linked in the non-genital forms. HPV-16 and HPV-18 have been associated with lesions on the palms (Fig. 10.32) and soles, particularly the verrucous variety, and around digits. These are all unusual sites for Bowen's disease. HPV may also be associated with disease in younger and in dark-skinned patients.

Clinical Features
Symptoms
A solitary rough patch, which is often misdiagnosed as eczema or psoriasis.

Morphology
There is a well-defined, very slightly raised, red plaque, with a rough adherent scale (Figs 10.33 and 10.34). It grows slowly. Pigmented and verrucous lesions are less common variants.

Distribution
The most common sites are the face (Fig. 10.35), backs of the hands and digits (Fig. 10.36), lower legs (usually women), and trunk (Fig. 10.37). If it is caused by ultraviolet light, the lesion is usually solitary. If arsenic is implicated, the lesions may be multiple and occur asymmetrically on the trunk. In addition keratoses may occasionally be found on the palms and rarely arsenic may cause a macular 'raindrop' pigmentation of the skin.

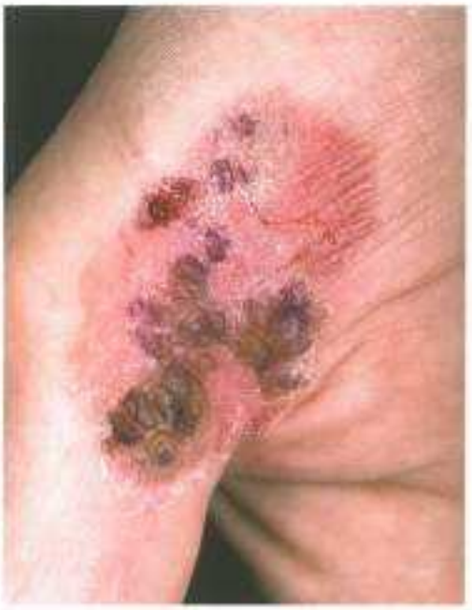


Fig. 10.32 Verrucous Bowen's disease. Occasionally a cutaneous horn may arise from Bowen's disease. Human papilloma virus types 16 and 18 have been isolated from this form.

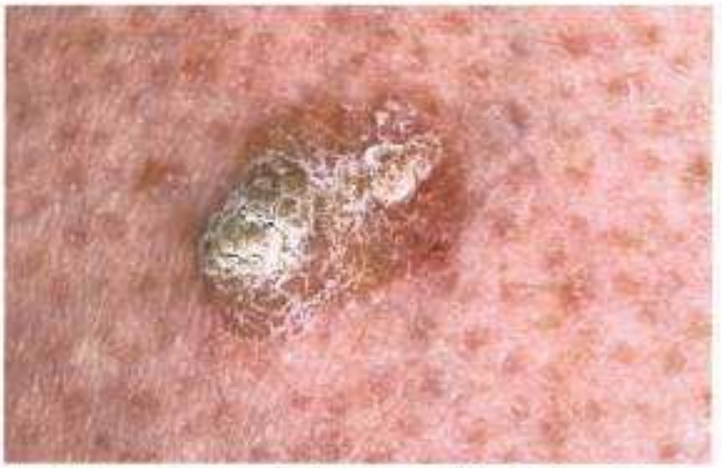


Fig. 10.33 Bowen's disease. The lesion is very well defined. It is a raised red plaque with a rough adherent scale or hyperkeratosis.

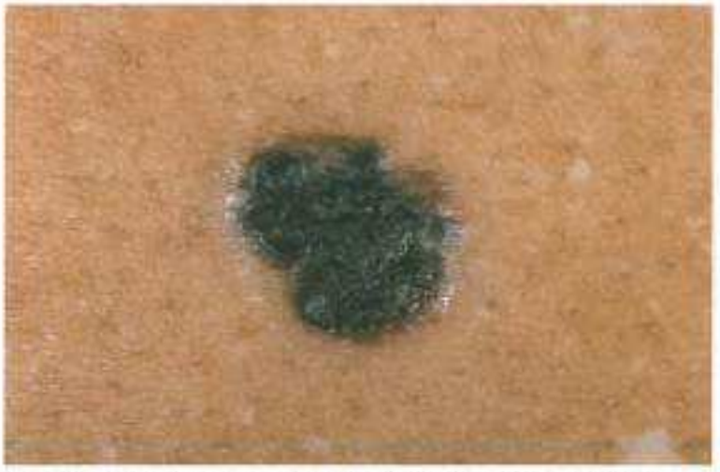


Fig. 10.34 Bowen's disease. This lesion proved on biopsy to be Bowen's disease. This is very rare in dark skin and there is almost always Celtic ancestry.

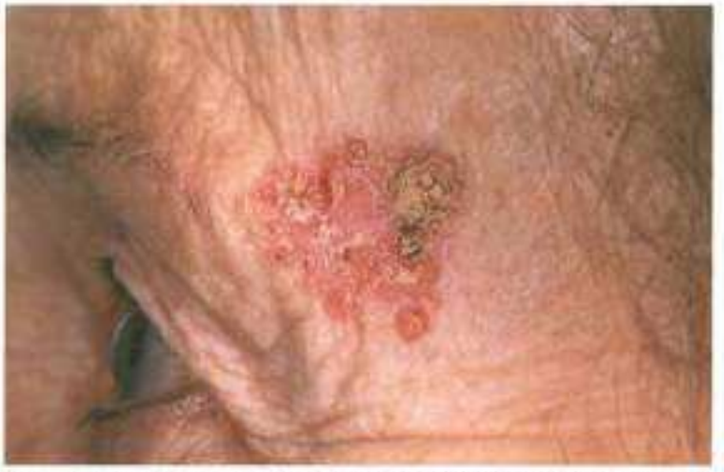


Fig. 10.35 Bowen's disease. This is an intraepidermal squamous cell carcinoma of the skin. Dermal invasion, however, is unusual. The face and lower legs are common sites.

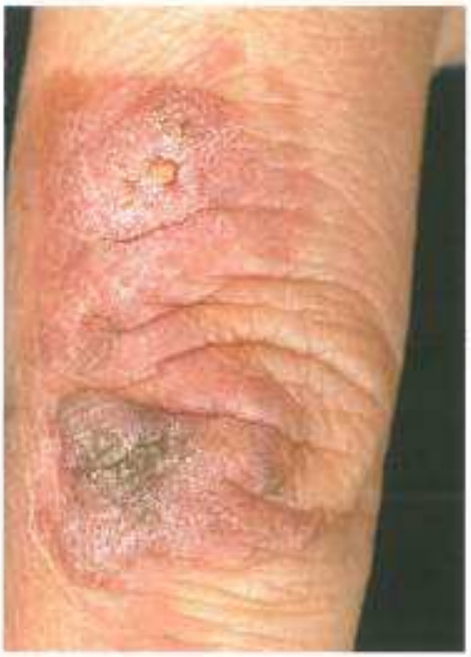


Fig 10.36 Bowen's disease. Bowen's disease occurs in sun-exposed sites including the backs of the fingers and hands and is frequently mistaken for eczema or psoriasis.

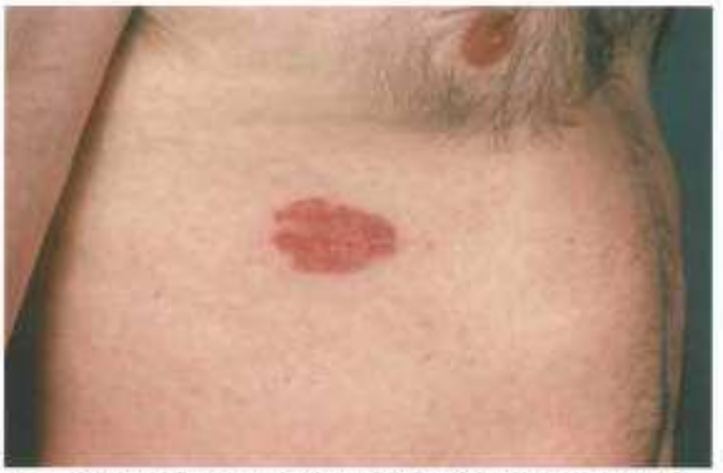


Fig. 10.37 Bowen's disease. There is a solitary plaque on the trunk shown to the author at a social function, an example of "kerbside dermatology". Subsequent biopsy showed intraepidermal carcinoma.

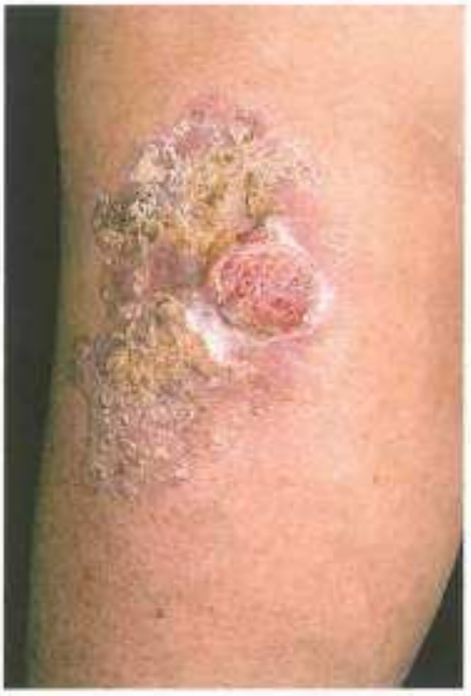


Fig. 10.38 Bowen's disease and squamous cell carcinoma. Intraepidermal carcinoma of the skin grows slowly and is often neglected. Squamous cell carcinoma ultimately develops.

Although the lesion is potentially a squamous cell carcinoma (Fig. 10.38), this is unusual. Malignant change is suggested if it becomes thicker, more indurated, eroded or ulcerated.

Histopathology

The histology of Bowen's disease is that of carcinoma in situ. There is parakeratosis, acanthosis and full-thickness dysplasia (Fig. 10.39). The epithelial architecture is completely disorganized. The pilosebaceous apparatus is characteristically involved, unlike in actinic keratoses. The cheeks are involved more in females, possibly because vellus hair follicles are more vulnerable than the masculine terminal hair follicles. There is loss of cellular maturation and orientation, nuclear and cytoplasmic pleomorphism and increased mitotic activity, both normal and abnormal, at varying levels within the epidermis. Occasionally, individual cell keratinization may be a feature and cytoplasmic vacuolation may be prominent (especially in arsenic-induced lesions).

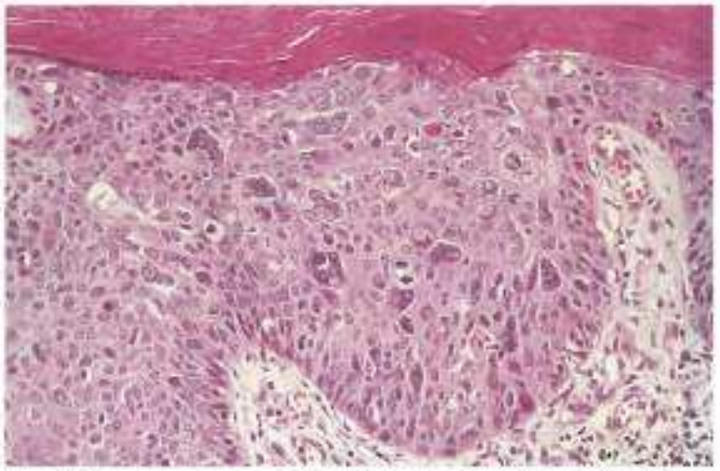


Fig. 10.39 Bowen's disease. There is massive hyperkeratosis and dysplasia throughout the thickened epidermis, with numerous pleomorphic and very enlarged nuclei. An abnormal mitotic figure is seen in the upper right quadrant.

Intraepidermal carcinoma of the genitalia

This is a squamous cell carcinoma in situ, i.e. Bowen's disease of the mucous membranes.

Aetiology

Bowen's disease may develop on the mucous membranes as well as on the skin but the terms *vulval intraepithelial neoplasia* (VIN) and *penile intraepithelial neoplasia* (PIN) are now used instead for Bowen's disease, Bowenoid papulosis and dystrophy with atypia. Lesions are graded. Bowen's disease of the vulva would be called VIN 3. Intraepidermal carcinoma is associated with HPV-16 and HPV-18 infection, particularly in multicentric and multifocal cases in younger patients, when it is associated with early onset of sexual activity, increased episodes of venereal disease (including HIV), immunosuppression and multiple sexual partners. Penile lesions (formerly known as *erythroplasia of Queyrat*) are most common in the uncircumcised, those with poor genital hygiene and smegma retention and in older patients in the developing world. Cases do, however, occur where there is no evidence of HPV infection, including following lichen sclerosus et atrophicus.

Clinical Features

Symptoms

A sore or itchy lesion on the vulva or glans penis.

Morphology

There is a well-defined and slightly raised red plaque, which may have a velvety texture.

Distribution

In the male, the intraepidermal carcinoma is confined to the glans penis (Fig. 10.40); in the female, it is usually on the labium majorum (Fig. 10.41). Occasionally multiple well-defined pigmented velvety plaques occur not only around the labia but also around the anus; this was formerly known as 'multicentric pigmented Bowen's disease' (Fig. 10.42) and was termed Bowenoid papulosis by Wade in 1979.

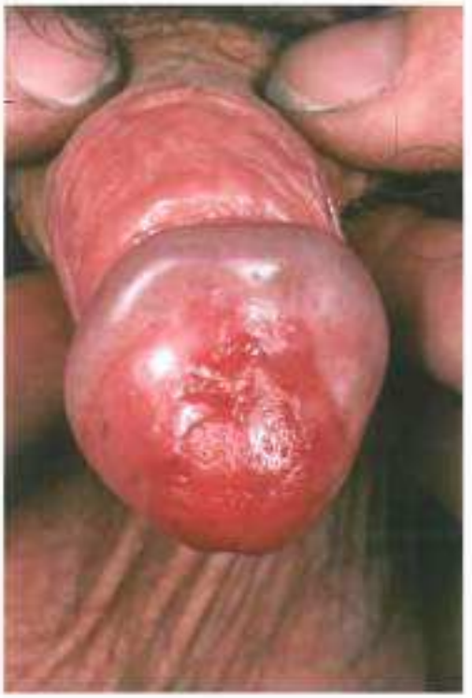


Fig. 10.40 Bowen's disease of the glans penis. Formerly known as erythroplasia of Queyrat, the lesion is a red, well-defined, slightly raised eroded plaque.

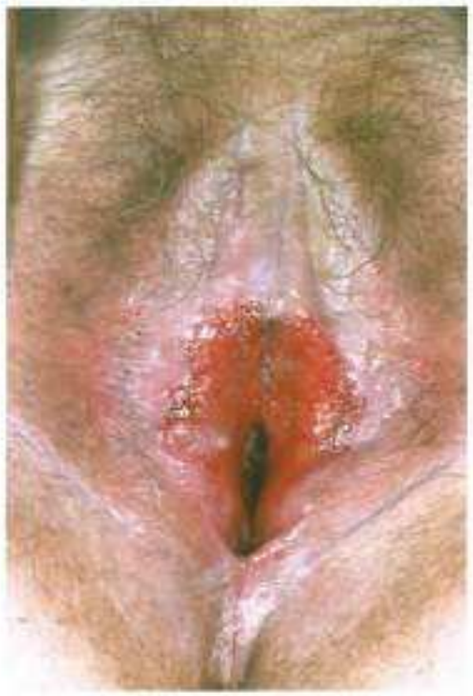


Fig. 10.41 Bowen's disease of the vulva. A raw, well-defined plaque of intraepidermal carcinoma has arisen around the urethra and introitus arising from lichen sclerosus et atrophicus.

Fig. 10.42 Bowen's disease of the vulva. There is a well-defined pigmented plaque on the labia and encroaching around the anus. A biopsy will quickly establish the diagnosis.

Bowenoid papulosis

Bowenoid papulosis is a genital disorder probably induced by oncogenic wart viruses; it has a premalignant histopathology.

Aetiology

The presence of HPV-16 and HPV-18 in these lesions has been established by molecular hybridization studies. Female patients often have cervical intraepithelial neoplasia in addition and female partners of affected males have HPV infection of the cervix. Bowenoid papulosis represents a high risk for cervical neoplasia for female patients and for sexual partners of affected males. Some, however, do not believe there is any justification for the distinction of Bowenoid papulosis from other forms of intraepithelial neoplasia, although it is generally regarded as a more benign process, behaving similarly to condyloma acuminata despite the fact that the histology reveals a carcinoma in situ.

Clinical Features

Symptoms

There are many pigmented spots on the genitalia.

Morphology

There are multiple, slightly raised, red-brown (Fig. 10.43) or pigmented (Fig. 10.44) papules or plaques.

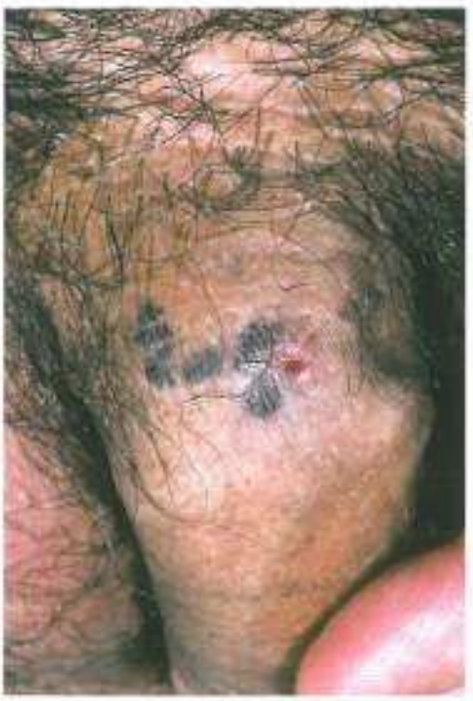


Fig. 10.43 Bowenoid papulosis. Multiple red-brown papules are present on the shaft of the penis. It may respond to conservative surgery, 5-fluorouracil or even undergo spontaneous regression.

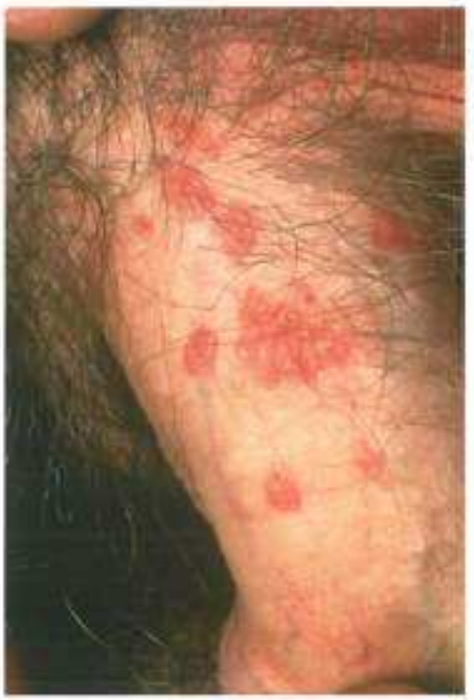


Fig. 10.44 Bowenoid papulosis. There are pigmented papules present that may look like warts until their true pathology is established on biopsy.

Distribution
The lesions usually affect the glans or shaft of the penis or the vulva, but in some patients there is involvement of the perianal region. Occasionally there may be hundreds of papules, and in females the vagina and ectocervix may be involved.

Histopathology
The papules are characterized by acanthosis associated with varying degrees of dysplasia that range from mild changes through to carcinoma in situ.

Keratoacanthoma

A rapidly growing benign tumour, simulating squamous cell carcinoma, which involutes spontaneously within 4 months.

Aetiology
Keratoacanthoma is quite common. It affects older age groups, particularly males. Chronic solar overexposure is the usual cause, but transplant recipients on long-term immunosuppressive drugs are prone, as well as individuals exposed to pitch and tar. There is growing evidence that it is associated with HPV-9 and is not a true malignancy. Unlike squamous cell carcinoma, mutations in p53 are rare.

There is a very unusual condition limited to two large Scottish families known as the *multiple self-healing epithelioma of Ferguson Smith*. The gene is mapped to 9q22-q31 and probably arose from a single mutation that occurred in the late 18th century. Histologically, the individual lesions are indistinguishable from early squamous cell carcinomas but they heal spontaneously leaving a crenellated scar. The condition starts in the second decade and affects solar-exposed skin.

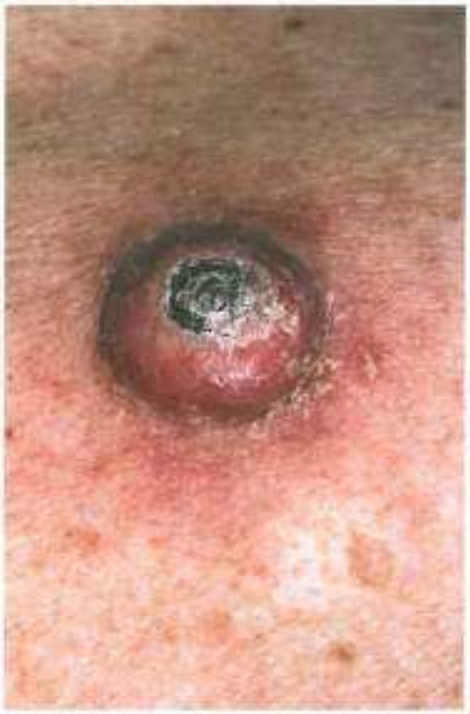


Fig. 10.45 Keratoacanthomas. The lesion evolves swiftly. It has a dome-shaped configuration with a keratin centre. This patient had had a liver transplant and was immunosuppressed. This lesion should be excised.

Clinical Features
Symptoms
It starts as a 'spot' and grows alarmingly and rapidly in size.

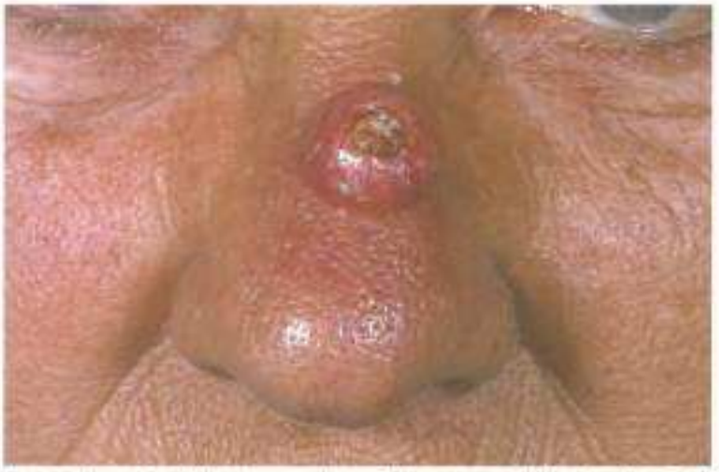
Morphology
The papule becomes a very well-defined uniform nodule, either red or flesh coloured. It stands proud and elevated (Fig. 10.45) away from the surrounding skin and has a central keratin-filled crater (Fig. 10.46). It is usually 1.5–2.0 cm in size but may be larger. It gradually accumulates more keratin and begins to involute and heal, leaving behind a pitted scar (Fig. 10.47). The whole process takes about 4 months.

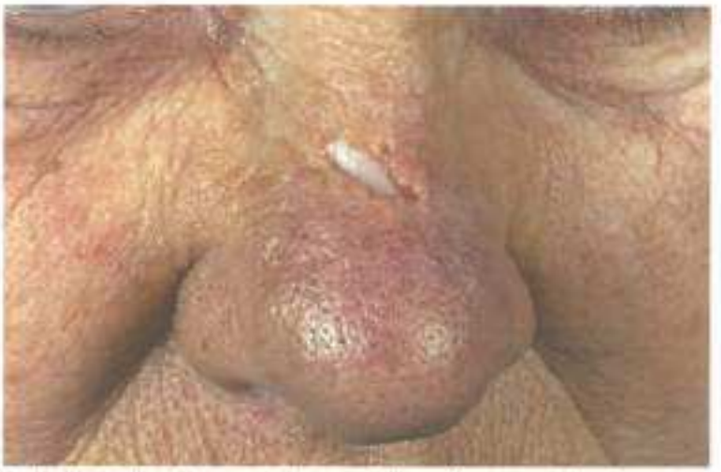
Distribution
Light-exposed areas: the face, particularly the nose, ears (Fig. 10.48) and cheeks, and the dorsum of the hands and forearms.

Histopathology
A fully evolved keratoacanthoma is flask shaped with well-developed lateral borders and a central keratin-filled epithelial invagination (Fig. 10.49). Although epithelial dysplasia may be present, more typically the proliferating epithelium is well differentiated, often with a ground-glass appearance (Fig. 10.50) and marked keratinization. In contrast to squamous cell carcinoma, where deep infiltration is usual, proliferation in keratoacanthoma is more marked along the lateral aspects of the lesion.

Management
Surgery

The lesion should be removed surgically. On the face they are often too large to remove surgically without major plastic repair, and curettage and cautery may be the preferred option. Certainly rapid referral may make management easier.





Figs 10.46 and 10.47 Keratoacanthoma. There is a well-defined nodule (Fig. 10.46) that is elevated from the surrounding normal skin and has a central keratin crater. The nodule resolved spontaneously to leave a pitted scar (Fig. 10.47).

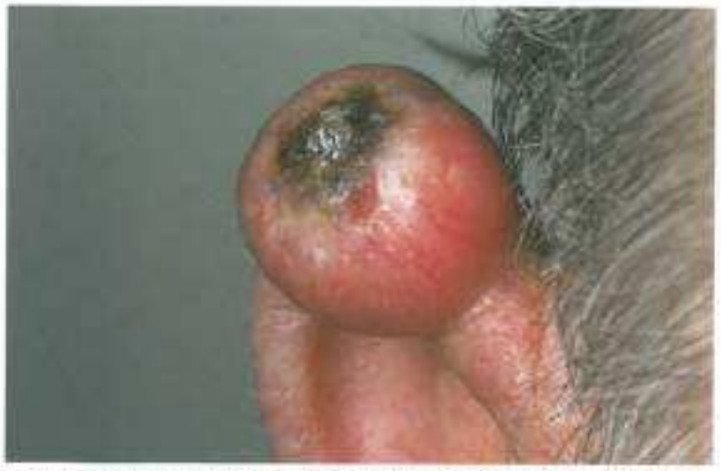


Fig. 10.48 Keratoacanthoma. The lesion is well circumscribed, grows rapidly and has a keratin centre. It favours light-exposed sites.

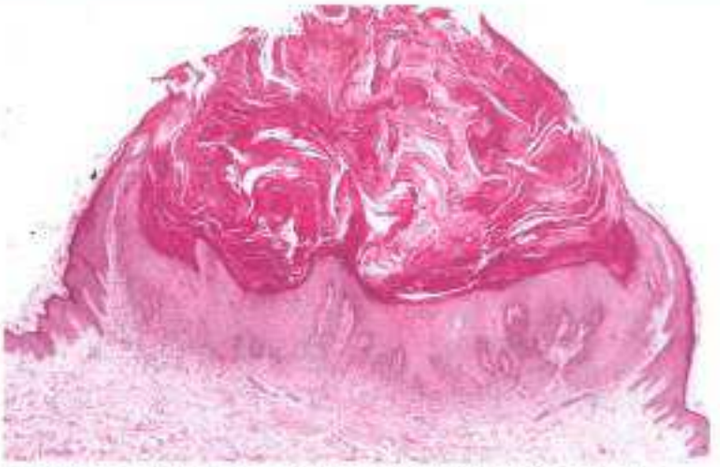


Fig. 10.49 Keratoacanthoma. This low-power view shows the keratin plug, filling the central invagination, with a well-formed lateral collarette.

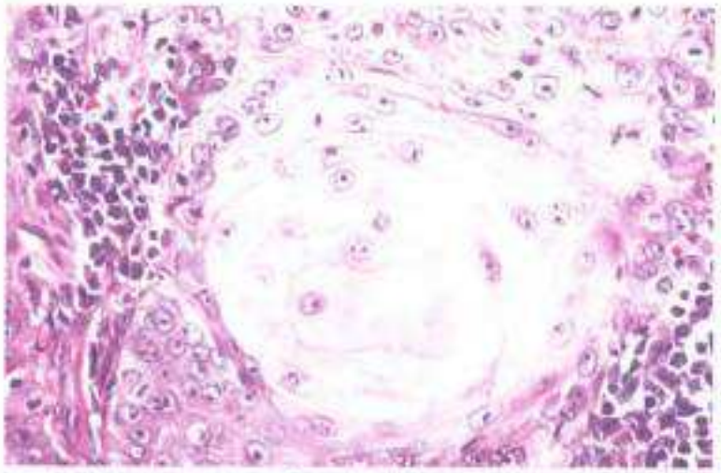


Fig. 10.50 Keratoacanthoma. Characteristically, in a well-developed lesion, the epithelium adopts a 'ground-glass' appearance. The dermis contains a heavy lymphocytic and plasma cell infiltrate.

Other treatments

Weekly doses of methotrexate can be helpful in speeding resolution of large keratoacanthoma not amenable to surgery. Radiotherapy may be considered, especially for giant aggressive keratoacanthomas.

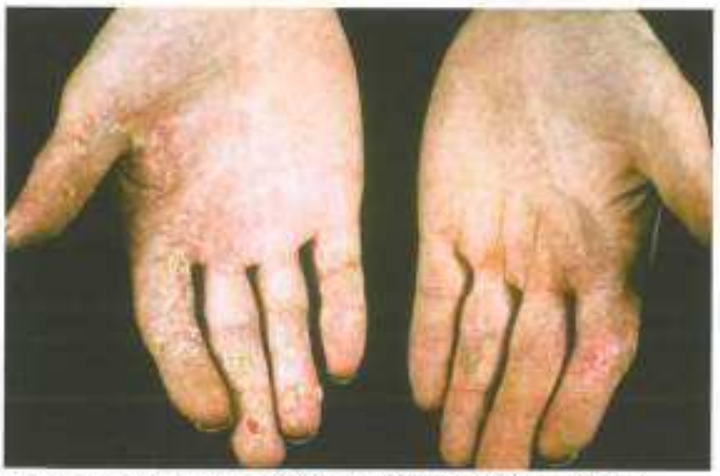
Squamous cell carcinoma

A malignant tumour arising from keratinocytes that may metastasize.

Aetiology

Squamous cell carcinoma is increasing in frequency in the UK. It is potentially dangerous since, after infiltrating locally, it may metastasize to lymph nodes and result in carcinomatosis. It is twice as common in males and tends to occur in older age groups. The incidence and aetiology varies in different parts of the world. The causes are:

- **X-ray irradiation** Before the danger of X-rays was appreciated, radiologists were at risk, particularly on the hands (Fig. 10.51). X-ray treatment of diseases such as psoriasis, ringworm (Fig. 10.52), acne and ankylosing spondylitis may be followed by the development of squamous cell carcinoma.
- **Ultraviolet irradiation** This is the most common cause in Caucasians. The highest incidences in the world are in Texas and Queensland. The lesion may start de novo in chronically sun-damaged skin and ultimately metastasize; alternatively, it may arise from a preceding solar keratosis or Bowen's disease, when metastasis is unusual.



Figs 10.51 Radiodermatitis. Careless use of X-ray equipment resulted in radiodermatitis of the hands of this dentist, a common occurrence before the hazards were appreciated. (Courtesy of Dr A. Wann, Institute of Dermatology.)

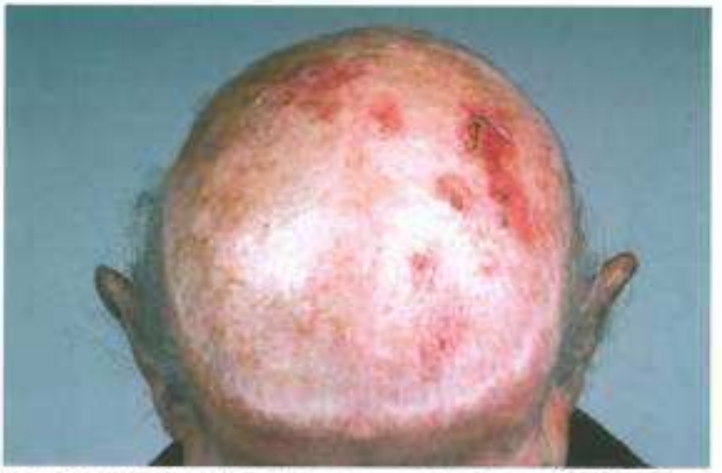


Fig. 10.52 Radiodermatitis and squamous cell carcinoma. The alopecia, atrophy and telangiectasia from radiotherapy for scalp ringworm in the 1930s is evident with several eroded crusted squamous cell carcinomas.

- **Polycyclic hydrocarbons** Tar, mineral oils, anthracene, pitch and soot are carcinogens to which individuals may be exposed in tar refineries, in road construction and in the production of briquettes and electrodes. The incidence of squamous cell carcinoma is falling because of better working conditions and improvements in personal hygiene. Percival Pott was the first to establish that soot caused squamous carcinoma of the scrotum in adults who many decades previously as children had ascended chimney stacks to sweep them. These agents are photosensitizers and may induce a diffuse hyperpigmentation of exposed sites (particularly the face), the Favre–Racouchot syndrome (cigarette smoke) and tar or pitch keratoses.
- **Arsenic** Previous arsenic ingestion may induce squamous cell carcinoma as well as Bowen's disease.
- **Scars** Squamous cell carcinoma may be a late sequela of any scarring process (Fig. 10.53). This includes those from burns or from skin diseases that result in scarring (e.g. epidermolysis bullosa, lupus vulgaris or, very occasionally, chronic varicose ulcers). A squamous cell carcinoma that arises in an ulcer on the lower leg is known as *Marjolin's ulcer* (Figs 10.54 and 10.55).
- **Certain genetic disease**
  - *Albinism* There is an enzymatic failure to produce the photoprotective pigment melanin. Keratoses and squamous cell carcinoma are common. Albinism is responsible for most cutaneous malignancies in patients with black skin. Interestingly, squamous cell carcinoma is unusual in vitiligo, a disease in which the melanocytes that produce the melanin are absent.
  - *Xeroderma pigmentosum* This is an enzyme deficiency which results in failure to repair DNA following solar injury. It results in the early evolution of skin cancer.
- **Mucosal skin diseases** Oral lichen planus and lichen sclerosus et atrophicus of the genitalia are very occasionally premalignant.
- **Human papilloma virus** HPV-16 and HPV-18 are oncogenic. They make a protein called E6 that inactivates p53. They are implicated in the development of squamous cell carcinoma of the genitalia. The *Buschke–Löwenstein tumour* (a term that is no longer used) refers to a well-differentiated low-grade variant of verrucous HPV 6 and 16 driven perianal carcinoma (syn. *giant condyloma acuminatum*) with a good prognosis.
- **Therapy with psoralen and ultraviolet light (PUVA)** Squamous cell carcinoma, including that of the male genitalia, occurs after prolonged photochemotherapy, particularly for psoriasis. Mutations affecting p53 occur that are characteristic of those associated with solar exposure rather than those of PUVA. PUVA is known to reduce immune surveillance and this may permit some population of cells harbouring pre-existing mutated p53 to develop. It is wise to avoid this therapy in patients who already show signs of sun damage.
- **Sunbeds and other forms of ultraviolet light** Regular sunbed therapy may increase the incidence of non-melanoma skin cancer including dysplastic keratoses of the feet and possibly melanoma. Ultraviolet light used to treat acne may subsequently induce malignant change.
- **Nitrogen mustard therapy** Topical nitrogen mustard is used to treat the early stages of mycosis fungoides. Squamous cell carcinoma of the male genitalia very occasionally results.
- **Immunosuppressants** Squamous cell carcinoma and keratoacanthoma are the most common malignancies occurring in immunosuppressed organ transplant recipients. They occur earlier and are more aggressive than those in non-immunosuppressed patients. They are often multifocal. In Queensland, 50% of patients who have received a kidney transplant (Figs 10.56 and 10.57) will develop non-melanoma skin

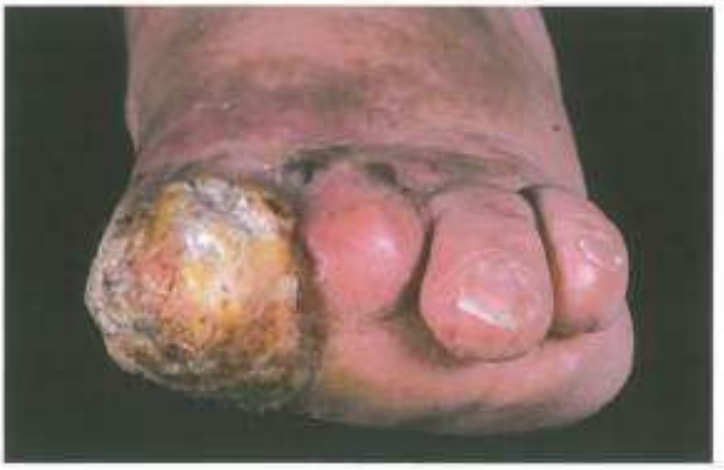


Fig. 10.53 Squamous cell carcinoma developing in a scar. This man had a skin graft following an injury. 40 years later he developed this lesion. A deep surgical biopsy established the diagnosis before the toe was amputated.

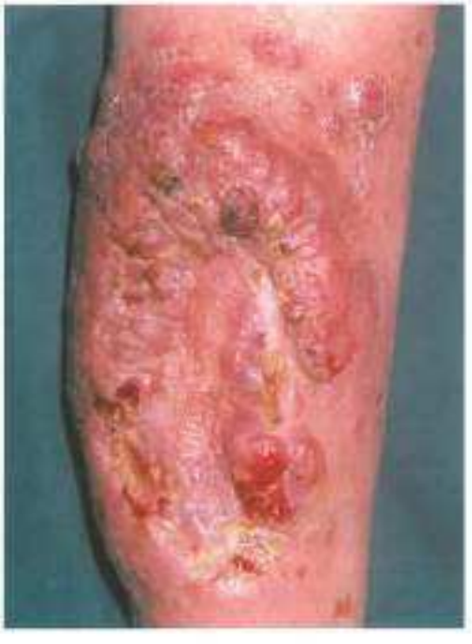


Fig. 10.54 Squamous cell carcinoma. Squamous cell carcinoma when it occurs on the lower leg is sometimes known as Marjolin's ulcer. This lesion failed to respond to nursing care and eventually was referred. The heaped-up margin of the lesion suggested the true diagnosis which was confirmed by biopsy.

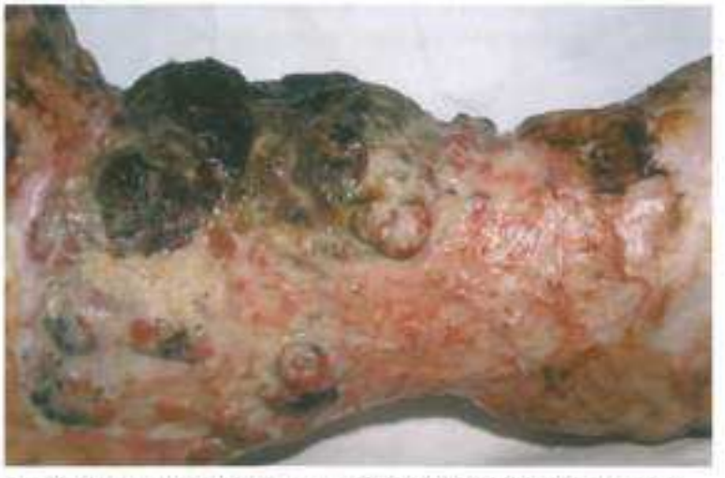


Fig. 10.55 Squamous cell carcinoma. Sadly, the occasional patient through ignorance, fear or psychological reasons neglects lesions on the skin. This patient died of her squamous cell carcinoma of the leg.

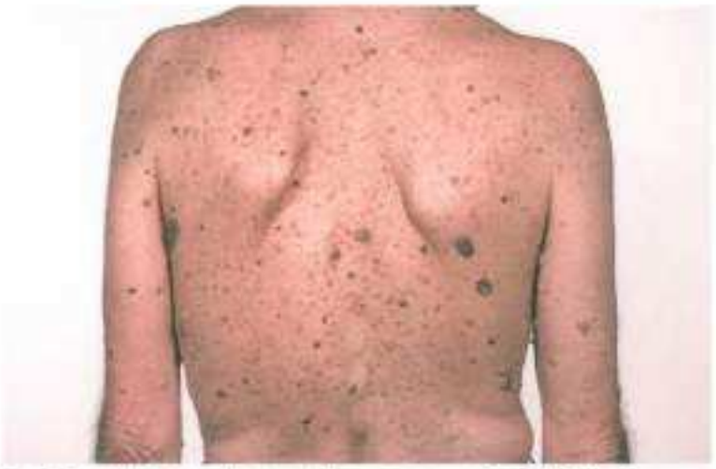


Fig. 10.56 Multiple keratoses and immunosuppression. Patients who receive organ transplants and require immunosuppressive therapy are highly likely to develop non-melanoma skin cancer. (Courtesy of Dr Elisabeth Higgins.)

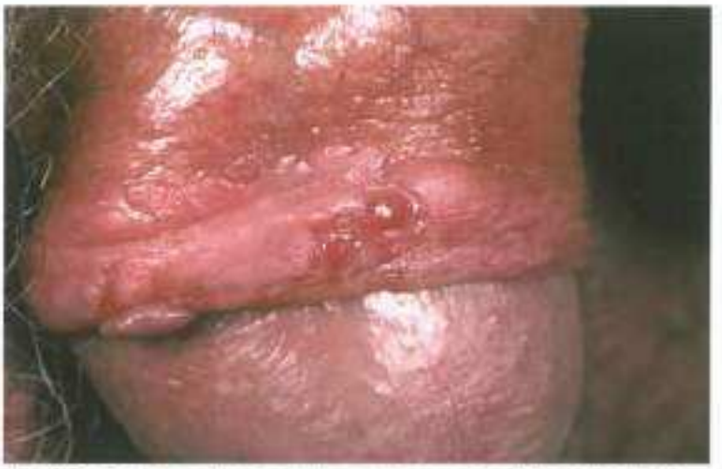


Fig. 10.57 Genital dysplasia and immunosuppression. This man had had a renal transplant. Similar lesions occur in patients taking azathioprine or ciclosporin long term for a variety of diseases.

cancer after 10 years and about 70% after 20 years of immunosuppression. The p53 mutation spectrum is similar to that in skin cancer induced by solar exposure. Males seem to be affected more than females. The head, neck and scalp are particularly vulnerable.

Clinical Features

Symptoms

A sore or ulcer that fails to heal.

Morphology

Squamous cell carcinoma starts as a thickening of the skin and becomes an indurated plaque. It grows laterally and vertically, gradually becoming fixed and nodular (Fig. 10.58). The surface may be crusted (under which is a purulent base), eroded (Fig. 10.59) or ulcerated. The margin is firm and more raised than that of a basal cell carcinoma (Fig. 10.60) and is often everted and irregular in shape. The lesion grows more rapidly than a basal cell carcinoma but not as fast as a keratoacanthoma.

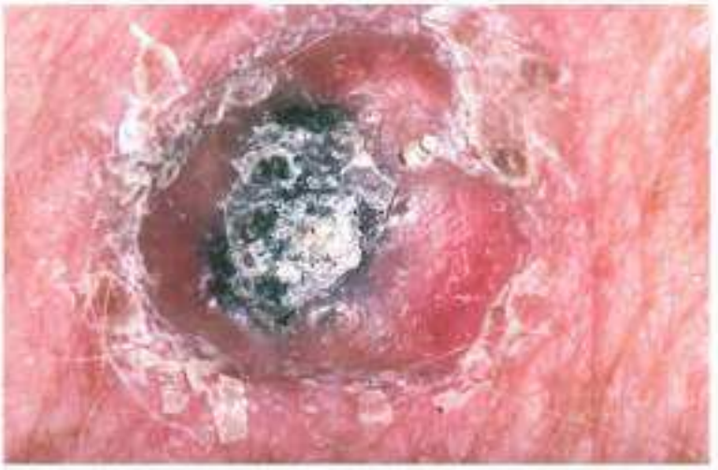


Fig. 10.58 Squamous cell carcinoma. The lesion starts as a nodule that subsequently becomes eroded, ulcerated and crusted as it grows.

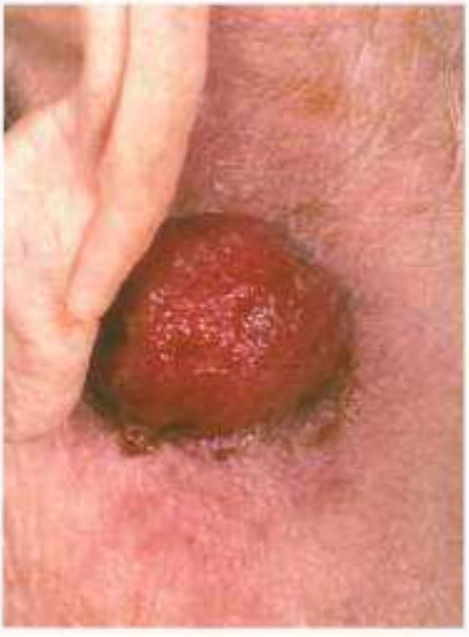


Fig. 10.59 Squamous cell carcinoma. There is a red nodule with a raw eroded surface. The skin behind the ear becomes photodamaged when the sun is behind the patient.

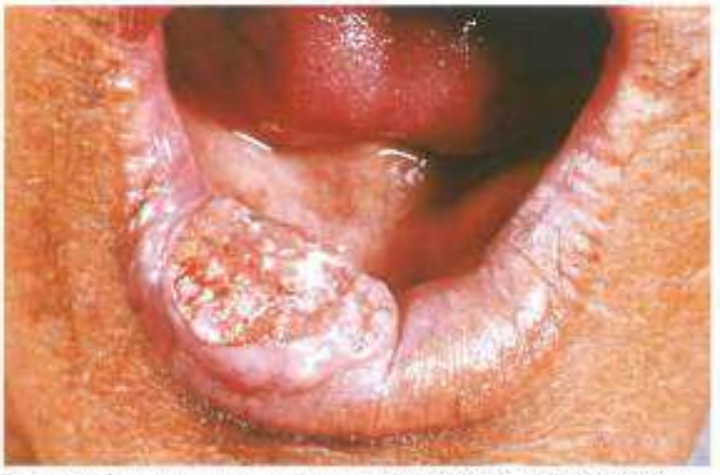


Fig. 10.60 Squamous cell carcinoma. The lesion is a well-defined ulcerated nodule with a heaped-up margin. The surrounding skin is white as a result of actinic cheilitis. (Courtesy of St Mary's Hospital.)

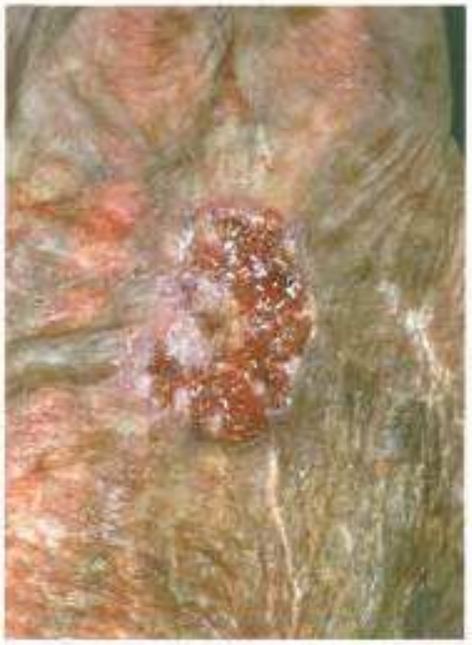


Fig. 10.61 Squamous cell carcinoma. The back of the hand is a common site for squamous cell carcinoma but not for basal cell carcinoma.

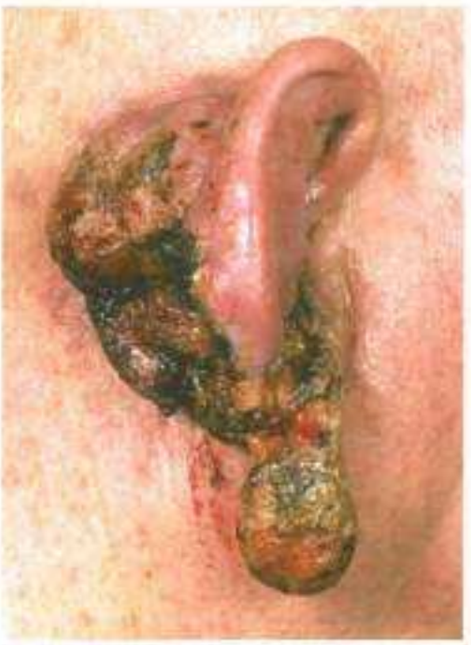


Fig. 10.62 Squamous cell carcinoma. This advanced nodular and ulcerated lesion metastasized to the cervical lymph nodes, chest and cervical vertebrae. The patient died 3 years after its excision.

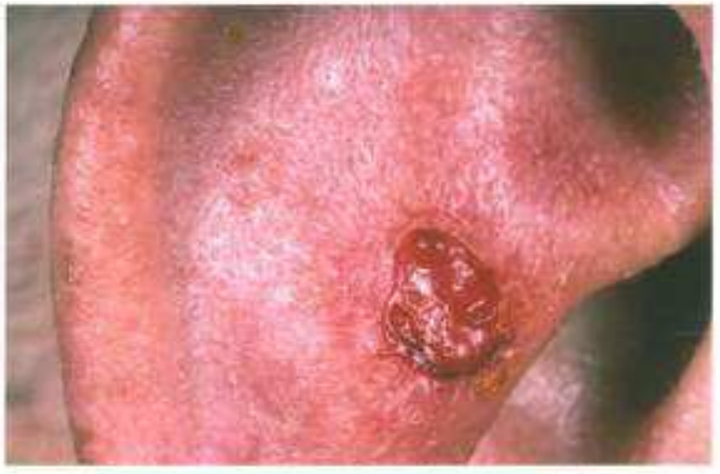


Fig. 10.63 Squamous cell carcinoma. The ear is a common site (and yet unusual for a basal cell carcinoma). There is a well-defined ulcer, which showed no signs of healing.

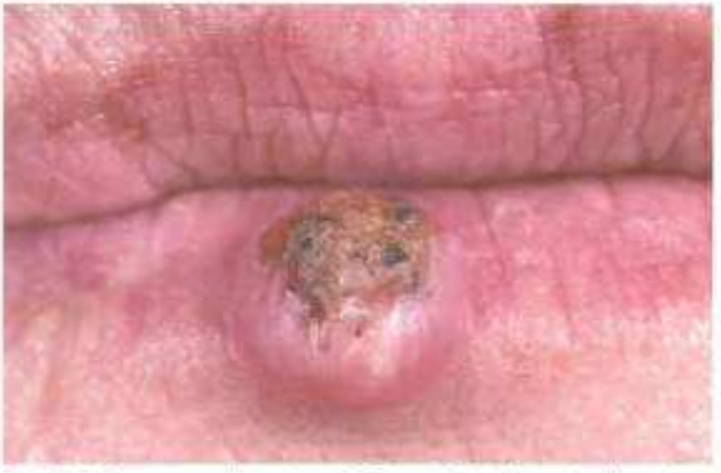


Fig. 10.64 Squamous cell carcinoma. The lower lip juts forward and is much more easily irradiated than the upper lip. Although simulating a keratoacanthoma, it grows much more slowly and this nodule proved to be a squamous cell carcinoma.

Distribution

Most squamous cell carcinomas occur on sun-exposed areas. The face, the extensor surfaces of the hands (Fig. 10.61), ears (Figs 10.62 and 10.63), lower lip (Fig. 10.64), forearms and lower legs are the most common sites. These are all unusual sites for a basal cell carcinoma, apart from the face. The surrounding skin usually has signs of actinic damage. Occasionally, a squamous cell carcinoma may occur in solar-protected skin such as around the genitalia and anus (Figs 10.65–10.67). A rare variant occurs on the sole of the foot (*epithelioma cuniculatum*).

The importance of squamous cell carcinoma is that it may metastasize to lymph nodes and end fatally (Fig. 10.68). Several factors govern prognosis.

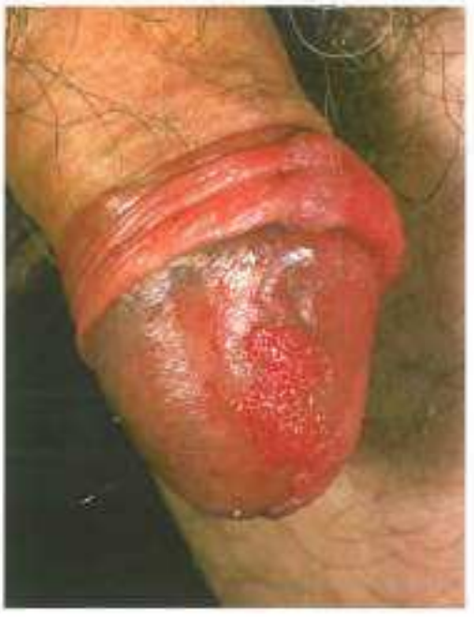


Fig. 10.65 Squamous cell carcinoma of the penis. A red raw vegetating warty plaque is present on the glans. Carcinoma rarely occurs in those circumcised early in life.

Fig. 10.66 Squamous cell carcinoma of the vulva. This vulval plaque in a 39-year-old female was VIN II with microinvasion.

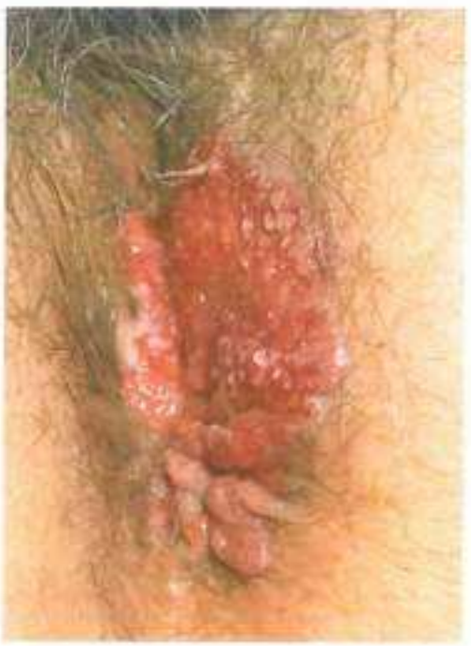


Fig. 10.67 Squamous cell carcinoma of the vulva. A vegetating, eroded, well-defined plaque of tumour is present.

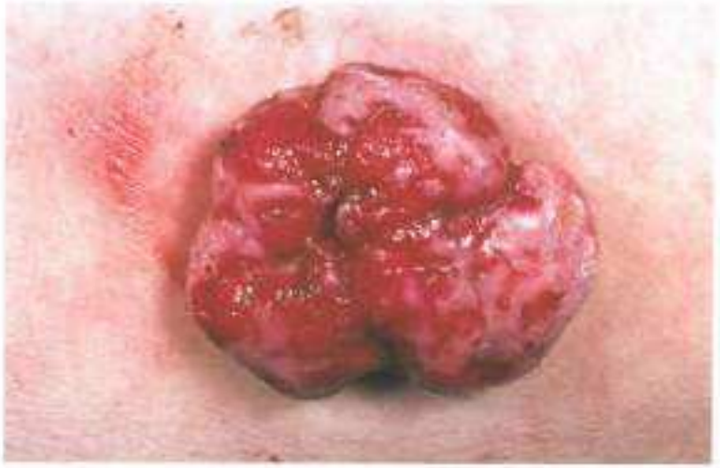


Fig. 10.68 Fatal squamous cell carcinoma. If neglected, the lesion grows inexorably and may metastasize via the lymphatics to the regional lymph nodes and systemically via the blood vessels.

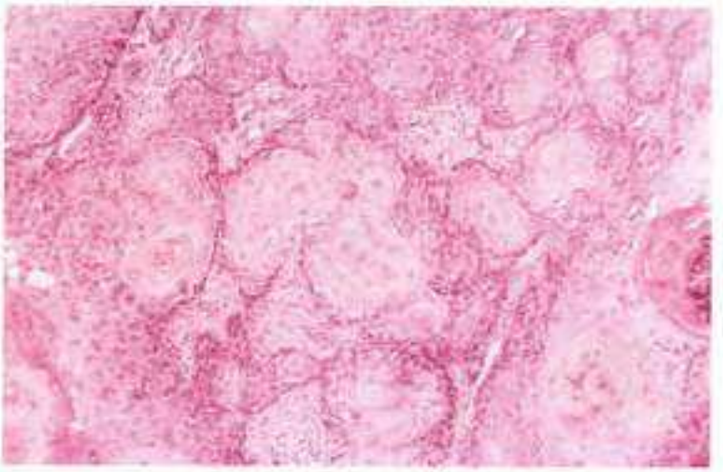


Fig. 10.69 Well-differentiated squamous cell carcinoma. The tumour is composed of readily recognizable squamous epithelium.

- **The preceding lesion** Squamous cell carcinomas arising in a solar keratosis or in cutaneous Bowen's disease rarely metastasize. Those that arise de novo or from other causes, for example chronic scarring disorders and X-ray irradiation, are more likely to do so.
- **Site** Lesions on the ear and the vermillion of the lip often metastasize. Those on the external genitalia and anus, including those that develop from mucosal Bowen's disease, also may metastasize.
- **Immunosuppression** Transplant recipients and those taking immunosuppressive agents such as azathioprine and ciclosporin for conditions such as rheumatoid arthritis develop lesions that are more aggressive, being locally more invasive and with a greater tendency to recur and to develop metastases.
- **Degree of differentiation** Clearly, a well-differentiated squamous cell carcinoma has a better prognosis than a poorly-differentiated one.
- **The depth of invasion** A tumour with a greater depth of invasion at the time of diagnosis has a poorer prognosis.

Histopathology

The appearances are variable and depend upon the degree of differentiation. Rarely, the tumour is so anaplastic that recognition of its precise nature is dependent upon detection of an epidermal origin.

Well-differentiated squamous carcinoma is typified by infiltrating islands of tumour that show obvious squamous differentiation (Fig. 10.69) with well-formed desmosomes and usually conspicuous and frequently abundant keratinization. Mitotic activity is usually not markedly increased and pleomorphism is minimal.

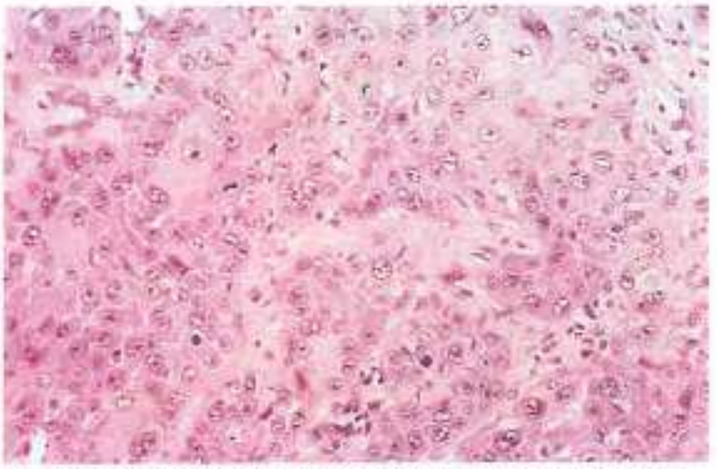


Fig. 10.70 Moderately differentiated squamous cell carcinoma. While the squamous nature of the tumour is still apparent, there is marked mitotic activity and nuclear pleomorphism.

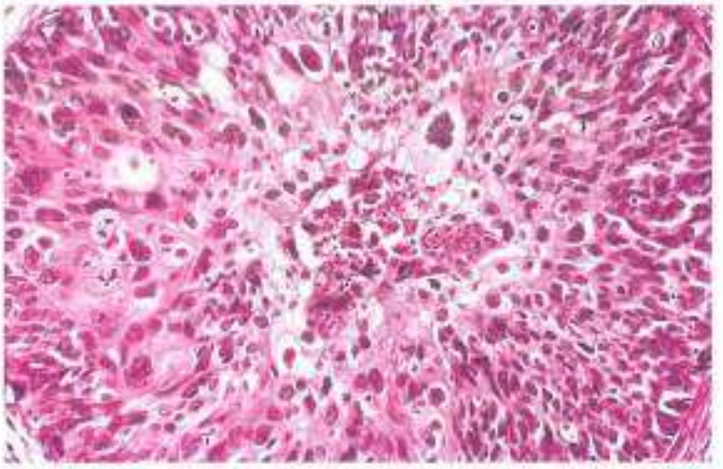


Fig. 10.71 Poorly differentiated squamous cell carcinoma. There is marked pleomorphism with hyperchromatic and sometimes bizarre nuclei and conspicuous mitotic figures. In the degenerate central region, scattered dyskeratotic cells are present.

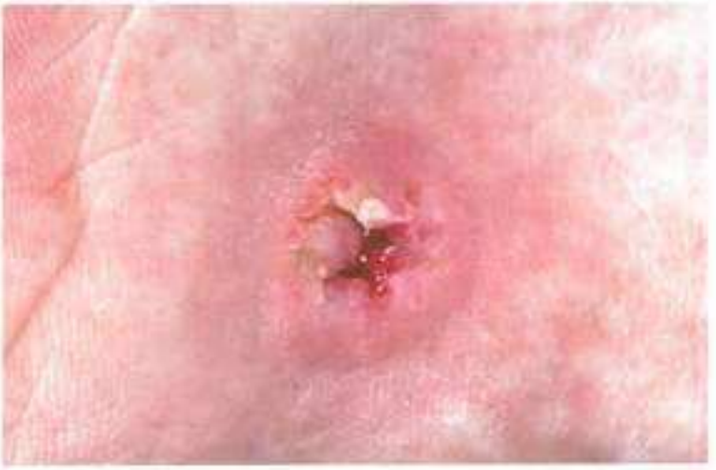


Fig. 10.72 Epithelioma cuniculatum. This is a squamous cell carcinoma of the sole of the foot. The lesion is frequently misdiagnosed.

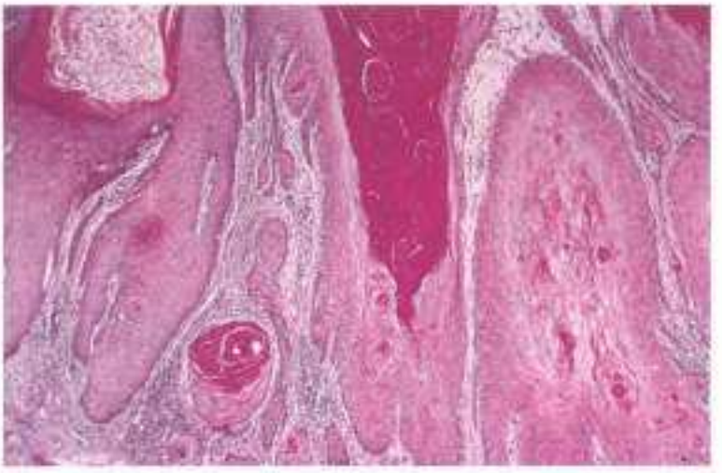


Fig. 10.73 Epithelioma cuniculatum. There is extensive permeation of the reticular dermis by downgrowths of very well-differentiated squamous epithelium. Note the extensive keratinization and characteristic blunt lower border of the tumour.

Moderately differentiated tumours are characterized by a more pleomorphic appearance with architectural disorganization, increased (and often abnormal) mitotic activity and imperfect keratinization; the latter is manifest as individual cell keratinization and keratin pearl formation (Fig. 10.70).

In poorly differentiated variants, there is marked pleomorphism (Fig. 10.71) and diagnosis is dependent upon detection of small foci of keratinization or occasional desmosomes.

Epithelioma cuniculatum on the sole of the foot (Figs 10.72 and 10.73) is characterized by an exceedingly well-differentiated histological appearance and a usually favourable outcome. Some may arise in pre-existent viral warts. The tumour is typified by the development of deeply penetrating, bulbous processes of well-differentiated squamous epithelium with marked keratinization.

Pseudoepitheliomatous hyperplasia (Fig. 10.74) is a histological entity that represents an extreme degree of acanthosis and may mimic squamous cell carcinoma. It is often seen in association with chronic venous stasis or chronic inflammatory disorders, including pyoderma gangrenosum, lupus vulgaris, syphilis and chromoblastomycosis.

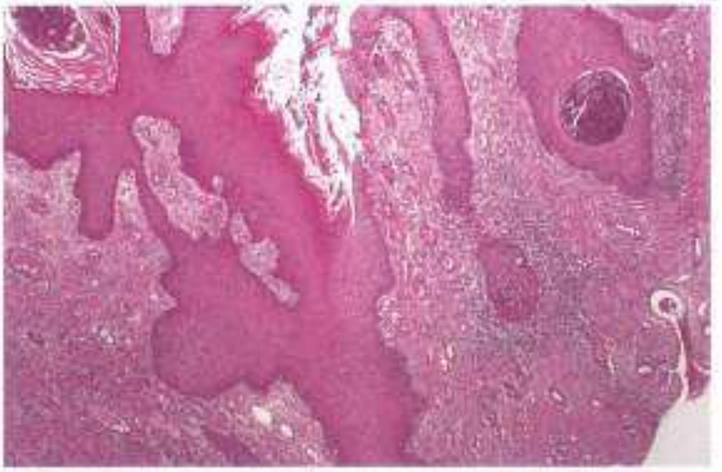


Fig. 10.74 Pseudoepitheliomatous hyperplasia. Islands of well-differentiated squamous epithelium extend deeply into the dermis. It must be distinguished from squamous cell carcinoma. The cause here was chromoblastomycosis.

Atypical fibroxanthoma

A malignant but non-metastasizing tumour of exposed irradiated fair skin.

Clinical Features

Symptoms

A sore that will not heal, usually in the elderly.

Morphology

A red fleshy plaque that becomes nodular and ulcerates.

Distribution

The head (Fig. 10.75) and face, particularly in association with sun damage and/or prior radiotherapy. It may occur on the limbs in a younger age group.

Histopathology

Atypical fibroxanthoma is a pleomorphic spindle cell tumour (Fig. 10.76) that resembles a malignant connective tissue neoplasm. It arises in the dermis and may invade the fat. There are atypical large fibroblastic and histiocytic cells, associated with multinucleate giant cells, lymphocytes and ectatic vascular spaces, any or all of which may show marked pleomorphism, hyperchromatism and prominent mitotic activity.

Management

The lesion should be adequately excised because it may recur, rather like dermatofibrosarcoma protuberans, but it does not metastasize.

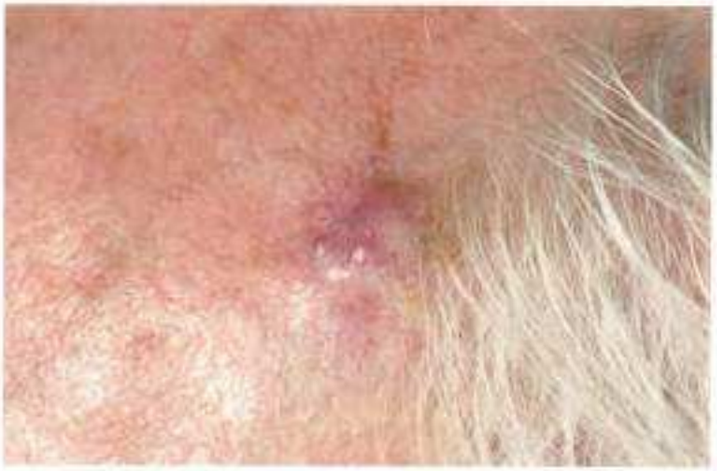


Fig. 10.75 Atypical fibroxanthoma. A nodule is present on a bald head, a typical site from solar damage. Although locally malignant and often recurring following surgery, it never metastasizes.

Basal cell carcinoma

A common, locally destructive, malignant cutaneous tumour derived from the basal cells of the lower epidermis. There are several clinical subtypes: the rodent ulcer, pigmented basal cell carcinoma, cystic basal cell carcinoma, morphoeic basal cell carcinoma, superficial basal cell carcinoma, fibroepithelial tumour of Pinkus and basal cell naevus syndrome (Gorlin syndrome), which are discussed below.

Aetiology

Basal cell carcinoma is the commonest malignant tumour of the skin. Although more prevalent following cumulative solar exposure and more common in skin types 1 and 2, ultraviolet light cannot be the sole explanation. Firstly, basal cell carcinoma is very common on the head and neck but unusual on other light-exposed areas, such as the backs of the hands and forearms, unlike solar keratoses and squamous cell carcinomas. Secondly, the inner canthus and eyelids, sites that are more shielded from sunlight than others on the face, are frequently involved. Thirdly, it does appear on solar-protected areas, such as the vulva. It may be that the basal cell layer of pilosebaceous follicles on the face is more susceptible to the effects of ultraviolet light. Pathologically, the tumour is composed of islands of basal cells, which originate from the basal cell layer of the epidermis and from adnexal structures, with a variety of histological appearances of variable differentiation. This reflects their probable derivation from undifferentiated epithelial germ cells.

Basal cell carcinomas may still be seen in patients who had ringworm of the scalp that was accidentally overtreated with X-ray irradiation many years previously. Patients treated for ankylosing spondylitis (Fig. 10.77) and lymphoma with X-irradiation may also develop basal cell carcinoma after a latent period of a number of decades.

Fig. 10.76 Atypical fibroxanthoma. A pleomorphic spindle cell tumour fills the dermis and abuts onto the basal cell layer of the epidermis.

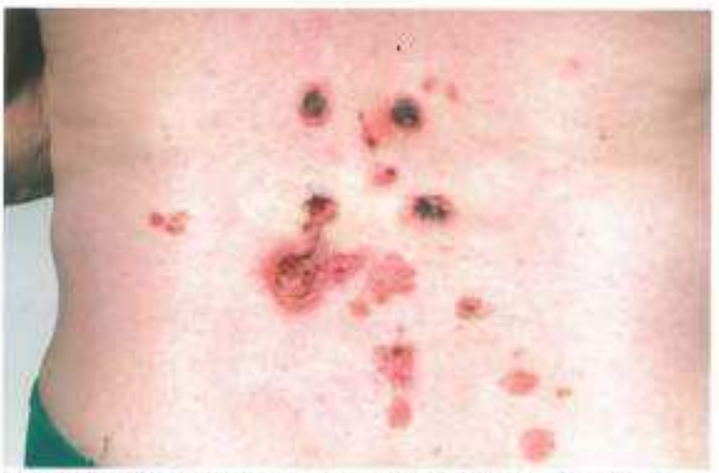


Fig. 10.77 Basal cell carcinomas. This man had radiotherapy for ankylosing spondylitis many years previously. These lesions developed subsequently and were mistaken for psoriasis associated with his joint disease until he sought a second opinion and a biopsy was performed.

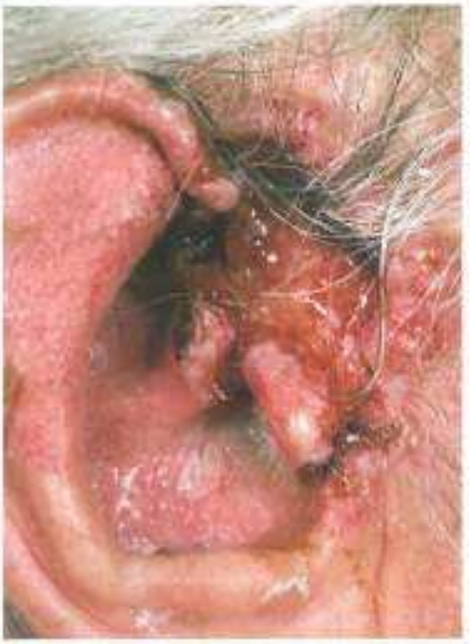


Fig. 10.78 Basal cell carcinoma.
This extensive and destructive 'rodent ulcer' illustrates the importance of early diagnosis. She was 86 and could not see very well and ignored it because it was painless.

Clinical Features

Symptoms

Patients often remark that the lesion tends to bleed, and subsequently scabs, but never quite seems to heal. Since it is painless and, therefore, considered to be harmless, it is sometimes ignored and allowed to grow to proportions that require complex therapy. This is particularly so in the elderly (possibly because they do not see the lesion well) and is becoming a considerable problem with an increasingly geriatric population.

The basal cell carcinoma rarely metastasizes but it is locally invasive and destructive. This is of particular importance when the lesion is situated near to the ear (Fig 10.78), eye (Fig. 10.79) or nose. If neglected (Fig. 10.80), the tumour may infiltrate deeply through tissue planes into the cranial cavity. Because of its location on the face, it should be possible to diagnose the lesion incidentally when the patient attends a physician for some unrelated problem.

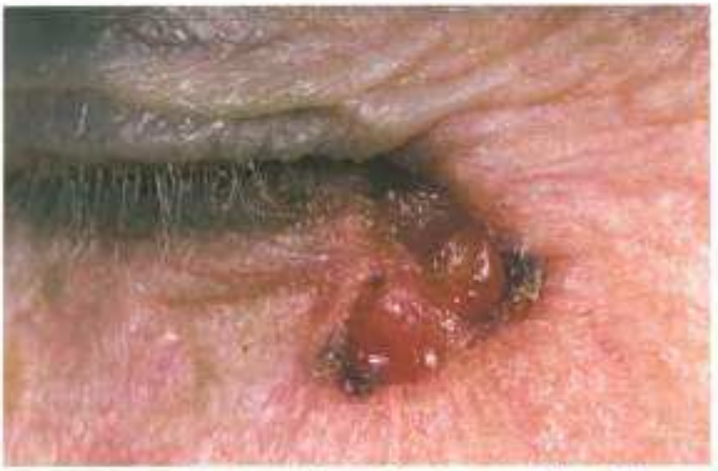


Fig. 10.79 Basal cell carcinoma. Basal cell carcinomas grow slowly but inexorably and if ignored, particularly in an important site near the eye, the situation in Figure 10.80 results.

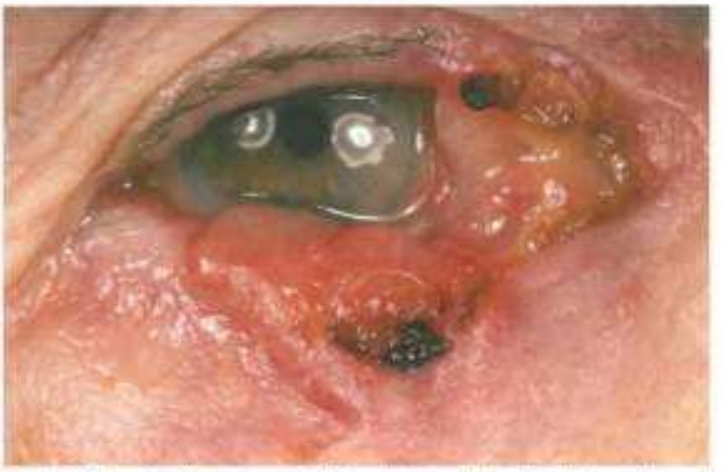


Fig. 10.80 Basal cell carcinoma. This 'rodent ulcer' illustrates the importance of early diagnosis. This octogenarian ignored the lesion because it was painless.

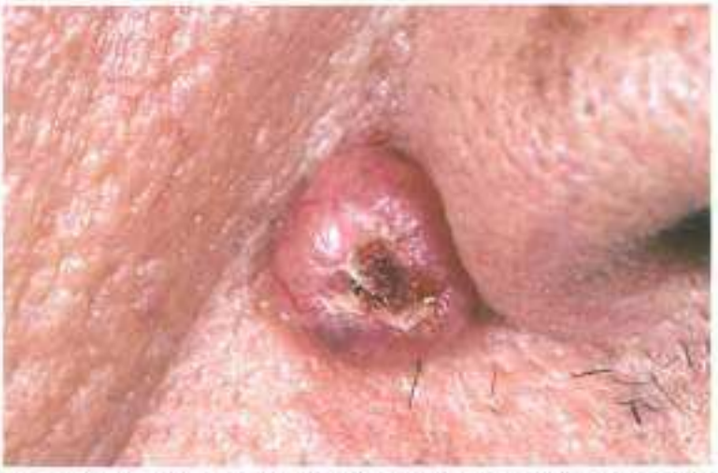


Fig. 10.81 Basal cell carcinoma. The margin is rolled and pearly in colour. There is pronounced telangiectasia and central ulceration. This is a typical *rodent ulcer*.

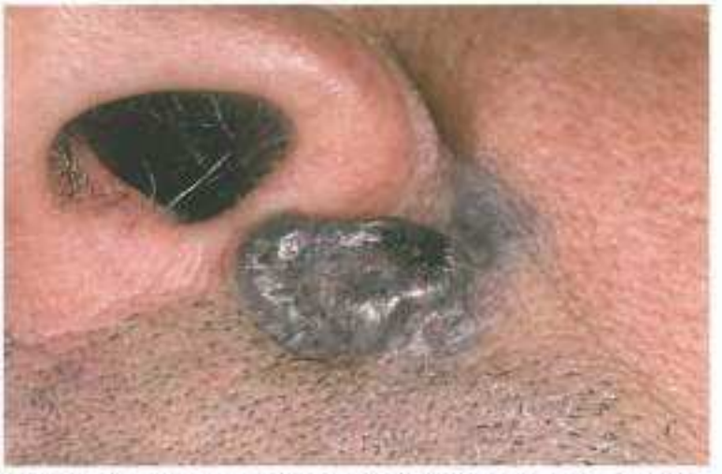


Fig. 10.82 Basal cell carcinoma. Basal cell carcinomas occur most usually on the face in Caucasians. It is very rare in black skin. This West Indian had a Scottish ancestor. It is very pigmented.

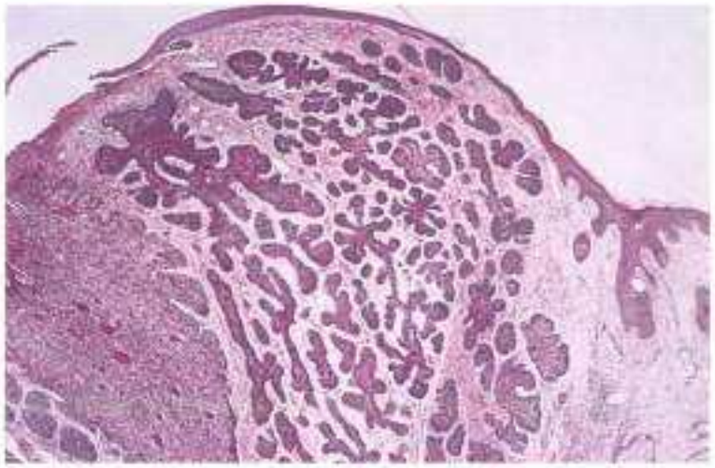


Fig. 10.83 Basal cell carcinoma. This low-power view shows extensive dermal invasion by discrete islands of small, darkly staining uniform cells.

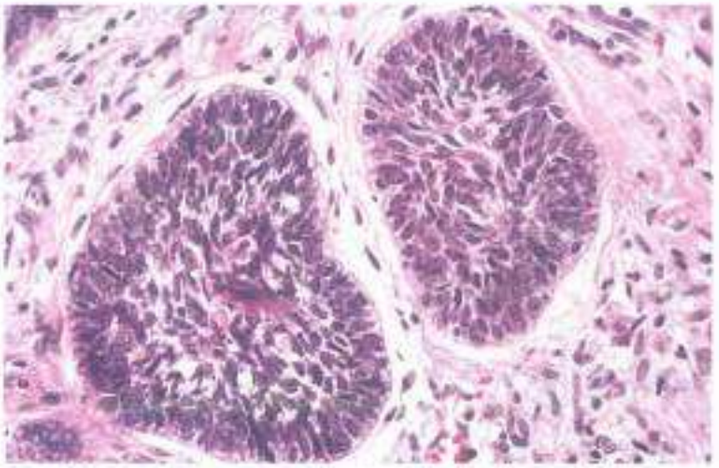


Fig. 10.84 Basal cell carcinoma. There is peripheral palisading of the tumour nuclei. The retraction around the tumour islands is a fixation artefact.

THE RODENT ULCER

Morphology

The rodent ulcer commences as a small papule, which subsequently becomes nodular and ulcerates centrally (Fig. 10.81). The margin of the ulcer is well defined, slightly raised and rolled, with a colour similar to that of a pearl. Tiny blood vessels (telangiectasia) may be seen coursing over this margin and this sometimes makes the lesion appear red. However, compression blanches the tumour and reveals the characteristic pearly coloration. It is rare in dark skin but the rolled margin is still evident (Fig. 10.82).

Histopathology

In its prototype form, the rodent ulcer is composed of discrete islands of small cells with darkly staining, uniform nuclei and scant ill-defined cytoplasm (Fig. 10.83). Peripheral palisading is a typical feature (Fig. 10.84). In most, but not all, instances, an origin from the overlying epidermis may be detected. The tumour islands are invariably accompanied by an actively proliferating connective tissue stroma. The latter appears to be an integral part of the tumour.

PIGMENTED BASAL CELL CARCINOMA

Morphology

The pigmented basal cell carcinoma has similar features to a rodent ulcer but the margins of the tumour are heavily pigmented (Fig. 10.85) and, consequently, may be mistaken for a malignant melanoma.

Histopathology

The pigmented basal cell carcinoma is characterized by dense deposits of melanin, which are found both within the tumour cells and as larger extracellular aggregates (Fig. 10.86). The significance of this pigmentation is uncertain.

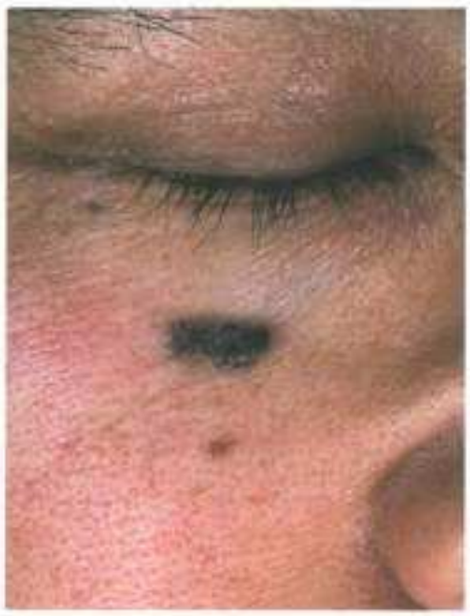


Fig. 10.85 Pigmented basal cell carcinoma. The lesion is quite pigmented and may be mistaken for a malignant melanoma but the rolled margin is characteristic.

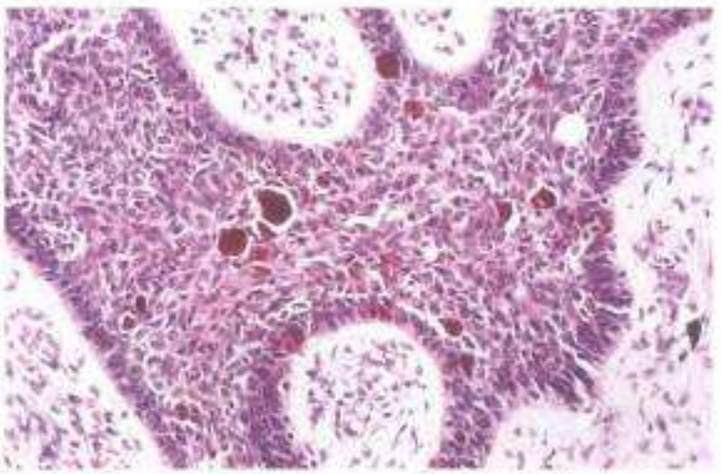


Fig. 10.86 Pigmented basal cell carcinoma. Dense deposits of melanin are present both within the tumour cells and as larger extracellular aggregates.

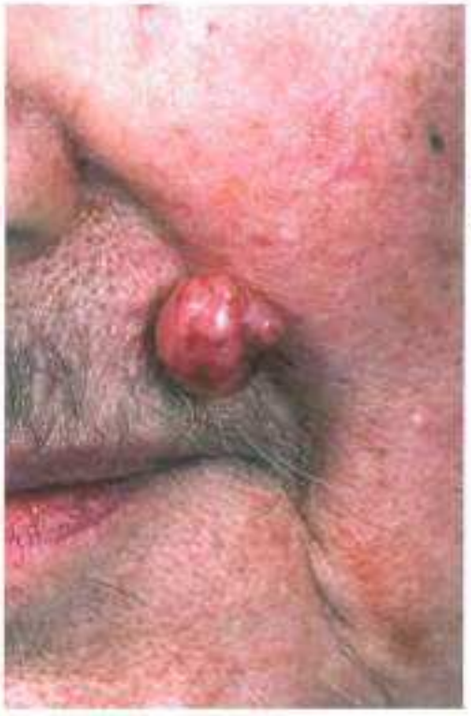


Fig. 10.87 Cystic basal cell carcinoma.
The lesion is often mistaken for a cyst and may become quite large before diagnosis. It is lobulated and vascular. The pearly colour is only demonstrable by blanching it.

CYSTIC BASAL CELL CARCINOMA

Morphology

In cystic basal cell carcinoma, the central part of the tumour does not break down and ulcerate until late in its evolution. It is a well-defined papule that gradually becomes a pearly coloured lobulated nodule with a smooth telangiectatic surface (Fig. 10.87). It often achieves a fair size and may be mistaken for a benign cyst.

Histopathology

Cystic foci are present (Fig. 10.88). In extreme examples, this may give rise to a generalized lacy pattern — so-called *adenoid basal cell carcinoma*. Whether this phenomenon occurs as a result of degenerative changes or is in reality a manifestation of sweat duct differentiation is uncertain.

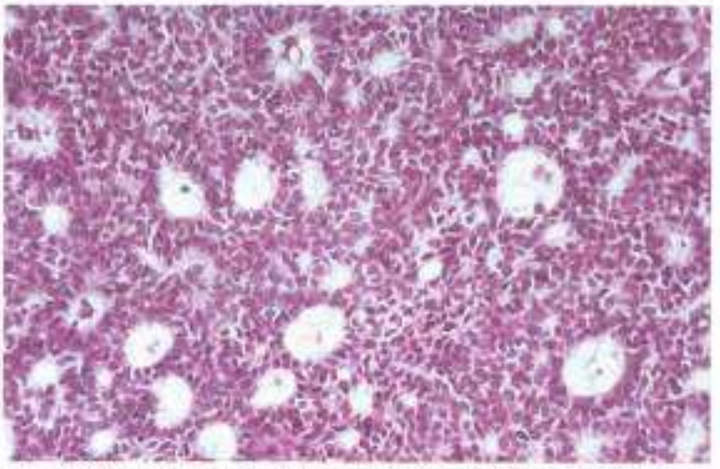


Fig. 10.88 Cystic basal cell carcinoma. This cystic pattern may be a focal change in a typical lesion, or represent the bulk of the tumour.

MORPHOEIC BASAL CELL CARCINOMA

Morphology

This is the most troublesome variant. It may be misdiagnosed as a scar, for it does not appear as a tumour but as a slightly elevated, smooth, firm plaque (Fig. 10.89). Indeed, the term 'morphoea' means sclerodermatous or hardened skin. Telangiectasia and the pearly colour are important features. The lesion spreads insidiously and is frequently diagnosed late (Fig. 10.90). Nests of tumour cells infiltrate well beyond the apparent clinical margins of the plaque, as well as deeply into the dermis and subcutaneous tissues. It can, therefore, be difficult to discern the limits of the tumour, so incomplete excision is not unusual.

Histopathology

Excessive connective tissue proliferation results in the morphoeic pattern (Fig. 10.91). Mitotic activity may be quite marked but this is not necessarily associated with any sinister implication. It is important to recognize those tumours that show an aggressive pattern of infiltration, with narrow tongues of epithelium that extend deeply into the adjacent connective tissue and beyond the apparent clinical margins.

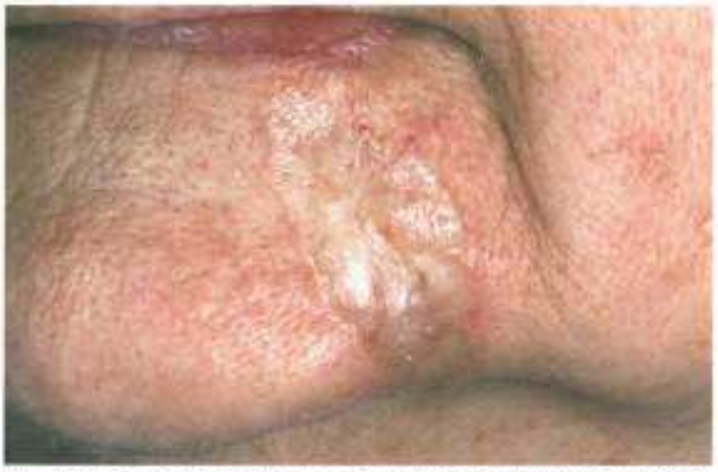


Fig. 10.89 Morphoeic basal cell carcinoma. The sclerodermatous (morphoeic) or scar-like appearance is well depicted here. It is a plaque rather than a papule or nodule and may present late.

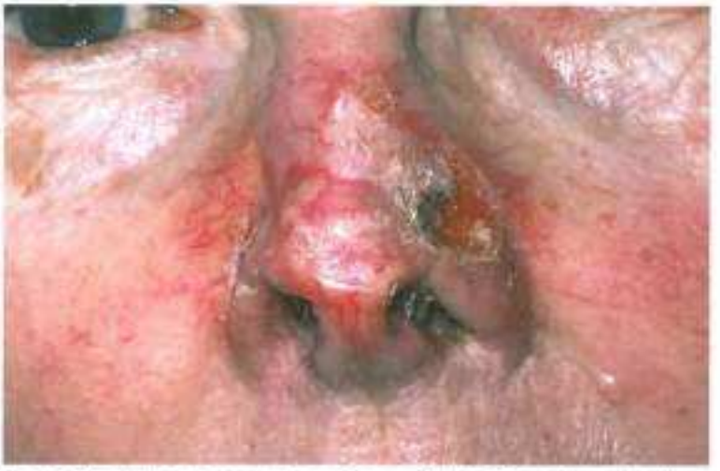


Fig. 10.90 Morphoeic basal cell carcinoma. The lesion is a plaque, rather than a nodule. Telangiectasia and ulceration are present and it is difficult to discern the margins. The lesion is extensive.

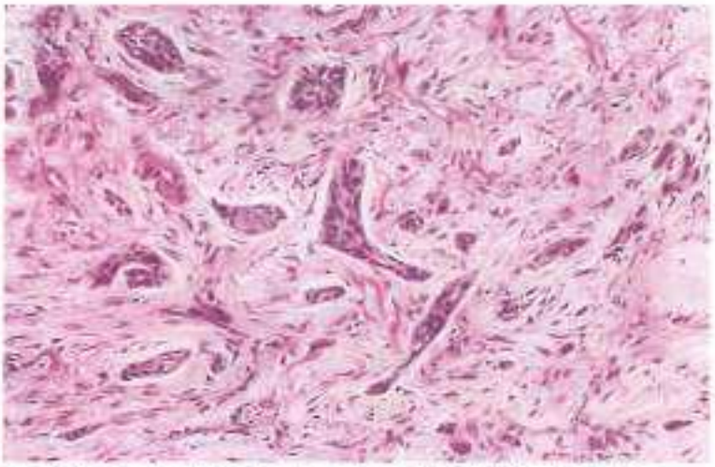


Fig. 10.91 Morphoeic basal cell carcinoma. In this tumour, the epithelial component is compressed into narrow strands by the intense fibroblastic stroma.

SUPERFICIAL BASAL CELL CARCINOMA

Clinical Features

Symptoms

A solitary patch on the trunk or limbs that is often mistaken for psoriasis or eczema.

Morphology

It is a well-defined slightly raised, red plaque with an adherent scale (Fig. 10.92). Careful inspection of its margin in a good light should reveal a very thin, rolled, telangiectatic pearly border (Figs 10.93 and 10.94). It may be pigmented (Fig. 10.95). Subsequently it thickens, becoming nodular and ulcerated.

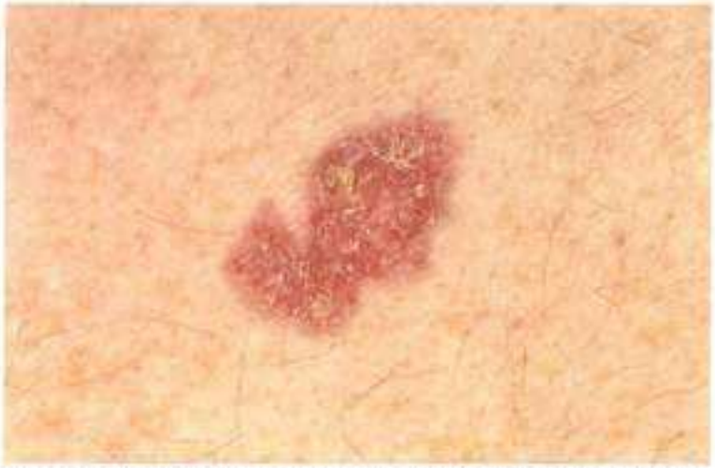


Fig. 10.92 Superficial basal cell carcinoma. A scaly red plaque is present that could be mistaken for psoriasis. However, the pearly margin gives away the diagnosis.

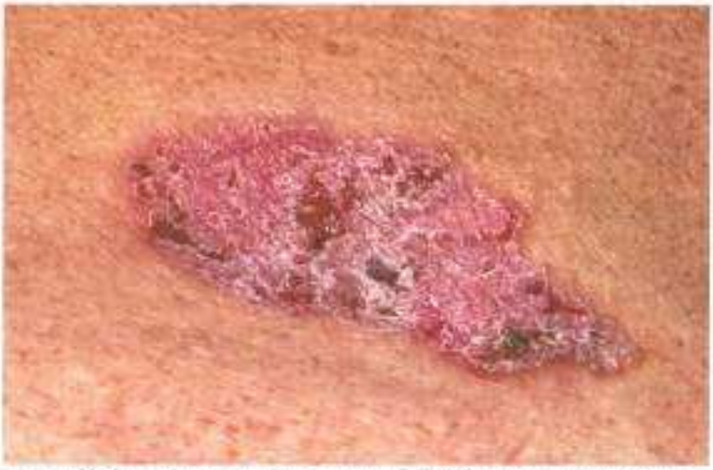


Fig. 10.93 Superficial focal cell carcinoma. This red, scaly plaque could be mistaken for psoriasis, but the rolled margin would suggest the correct diagnosis.

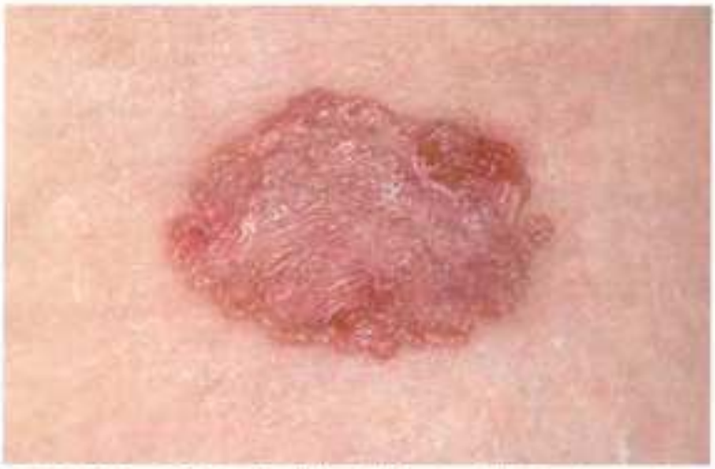


Fig. 10.94 Margin. The border of this well-defined, red, slightly scaly plaque has a distinct rolled pearly edge. It is a *superficial basal cell carcinoma*.

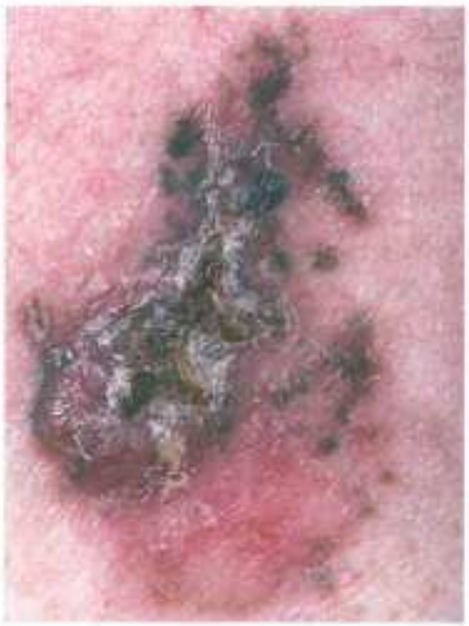


Fig. 10.95 Pigmented superficial basal cell carcinoma. Part of the margin is deeply pigmented. The lesion has invaded and become nodular at one edge.

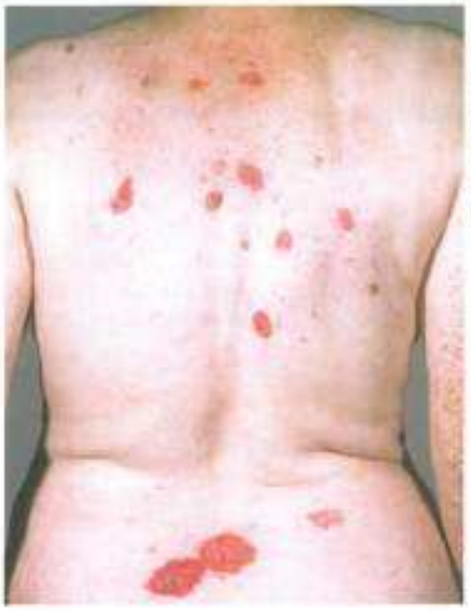


Fig. 10.96 Multiple superficial basal cell carcinomas. The lesions often simulate psoriasis and indeed may occur in patients given arsenic for their psoriasis. Note the asymmetry of the lesions, which is unlike psoriasis.

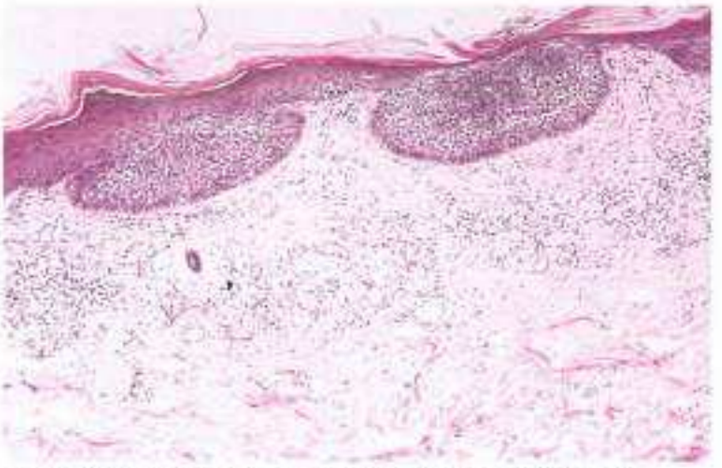


Fig. 10.97 Multifocal basal cell carcinoma. Two discrete foci of basaloid proliferative change budding off from the epidermis are present.

Distribution
Superficial basal cell carcinoma is usually solitary on the trunk or limbs. Multiple lesions result from previous arsenical therapy (Fig. 10.96), considerable ultraviolet exposure or radiotherapy (see Fig. 10.77).

Histopathology
The lesion is called superficial because of its pathological appearance. There are buds of multiple discrete foci of tiny basal cell carcinomas (Fig. 10.97), often still attached to the epidermis but dipping into the superficial dermis. Although on examination of a single section they appear separate, serial sectioning reveals an interconnected arborizing tumour. It can be difficult to determine the precise lateral limits of a superficial basal cell carcinoma.

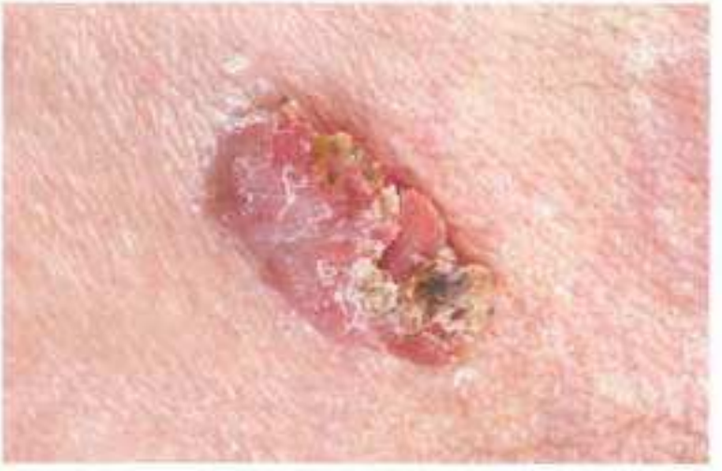


Fig. 10.98 Fibroepithelial tumour of Pinkus. A well-defined red nodule with a rough surface is present in the lumbar region. (Courtesy of Professor Hywel Williams.)

FIBROEPITHELIAL TUMOUR OF PINKUS
A relatively uncommon tumour, which may be a variant of a basal cell carcinoma but often associated with previous radiotherapy.

Clinical Features
Symptoms
An indolent plaque on the skin.

Morphology
This lesion is usually associated with superficial basal cell carcinomas and basal cell papillomas and is often mistaken for them. It is a well-defined papule or nodule with a red warty surface (Fig. 10.98).

Distribution
It may be single or multiple and occurs on the trunk, especially the lumbosacral region (particularly after radiotherapy for ankylosing spondylitis).

Histopathology
There are long thin branching strands of basaloid epithelial cells that are about two to three cells thick. They anastomose and encompass the fibrous stroma to produce a complex reticulate pattern (Fig. 10.99). Cyst and primitive hair-germ formation may occur. Rarely, it may develop into an invasive basal cell carcinoma.

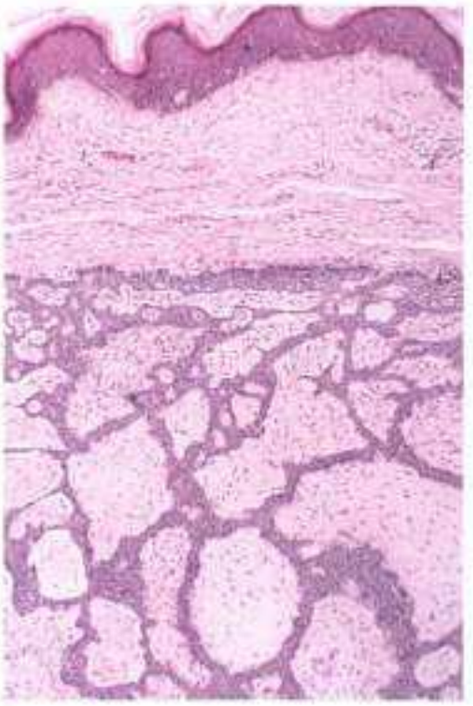


Fig. 10.99 Fibroepithelial tumour of Pinkus. Arising from the epidermis are multiple strands of basaloid epithelial cells that have anastomosed to create a complicated net-like pattern.

Management
The lesion should be excised.

BASAL CELL NAEVUS SYNDROME

An inherited condition of multiple basal cell carcinomas; it develops from childhood onwards and is associated with a variety of other abnormalities.

Aetiology

Basal cell naevus syndrome (*Gorlin syndrome*) is inherited as an autosomal dominant condition with variable penetrance. There is a germline mutation in the PTCH gene, a tumour suppressive gene on 9q22.3-3.1 and the human homologue of the *Drosophila* fruit fly patched gene. PTCH encodes a receptor that binds and acts in opposition to the sonic hedgehog ligand (a member of the hedgehog signalling family). It normally inhibits smoothend, causing tumour suppression but it is unable to do so when mutated which leads to nuclear transcription and tumour proliferation.

Clinical Features

Symptoms

Disfiguring lesions, developing early in life.

Morphology

The morphology is that of a basal cell carcinoma. There are pits to be found in the palms (Fig. 10.100) and soles and an array of milia, cysts, lipomas and fibromas on the skin.

Distribution

Predominantly on the face (Figs 10.101 and 10.102), but also on covered areas.

Systemic features

There is a characteristic facies in some patients of a broad nasal root with frontal bossing and hypertelorism. Bone abnormalities are common, with cysts in the jaw, defective dentition and the occasional development of ameloblastoma of the jaw. The ribs may be bifid and there may be brachymetacarpalism. There are ocular abnormalities such as strabismus, congenital blindness, cataracts and glaucoma. Neurological abnormalities include mental deficiency, calcification of the dura, medulloblastoma and congenital hydrocephalus. Ovarian fibromas occur in females and hypogonadism is not uncommon in males.

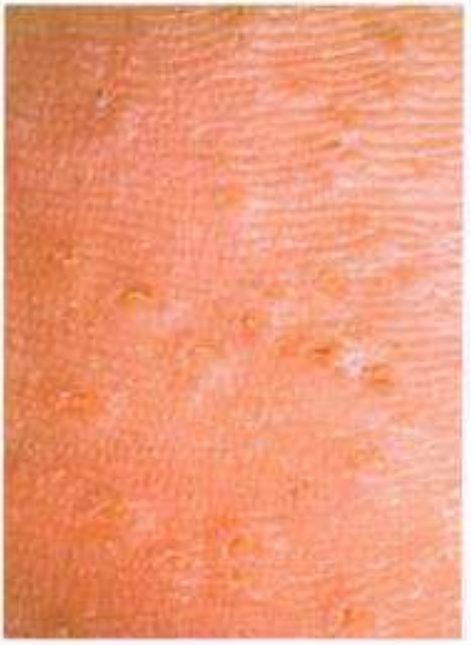


Fig. 10.100 Basal cell naevus syndrome. Tiny pits on the palms are characteristic additional features. (Courtesy of Dr Eugene van Scott, Skin and Cancer Hospital, Philadelphia.)

Management

The tumours of basal cell naevus syndrome are dealt with in the usual way for basal cell carcinoma, although X-ray irradiation should be avoided. Careful follow-up is required to deal with lesions in their early stages. Prenatal diagnosis has been described. The major criteria for diagnosis are multiple basal cell carcinomas, young onset, odontogenic keratocysts, palmar/plantar cysts, bifid, fused or markedly splayed ribs and similar findings in first-degree relatives. Minor criteria are macrocephaly, congenital malformations (cleft lip/palate, frontal bossing, coarse facies and hypertelorism), other skeletal abnormalities (Sprengel and pectoral deformity and syndactyly), ovarian fibromas and medulloblastomas. Experimental drugs (GDC-0449) which inhibit the hedgehog signalling pathway by *interacting* with smoothend are being assessed.

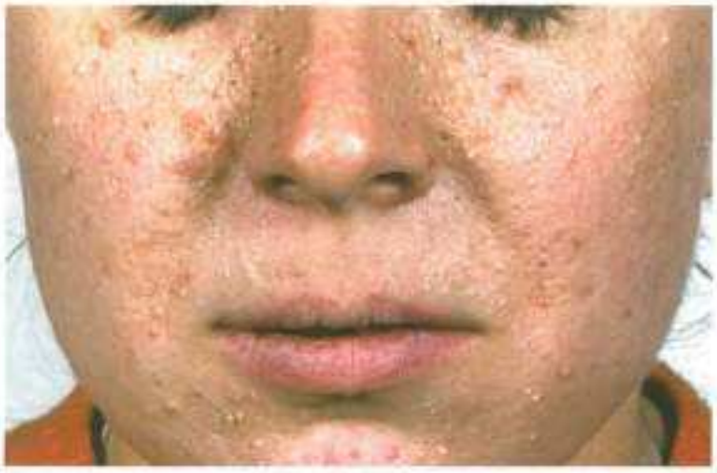


Fig. 10.101 Basal cell naevus syndrome. Multiple basal cell carcinomas develop from childhood onward. The condition is inherited as an autosomal dominant. (Courtesy of Dr A.C. Pembroke.)

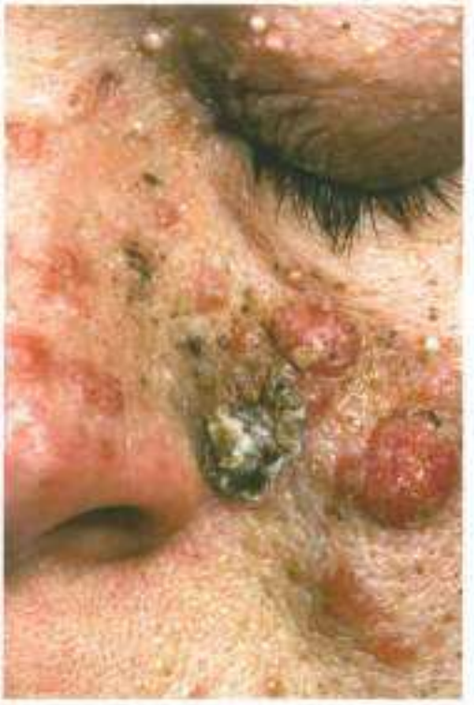


Fig. 10.102 Basal cell naevus syndrome. This is the same patient as in Fig. 10.101, who was lost to follow-up for some years. Large basal cell carcinomas are present. The milia and comedones are also prominent.

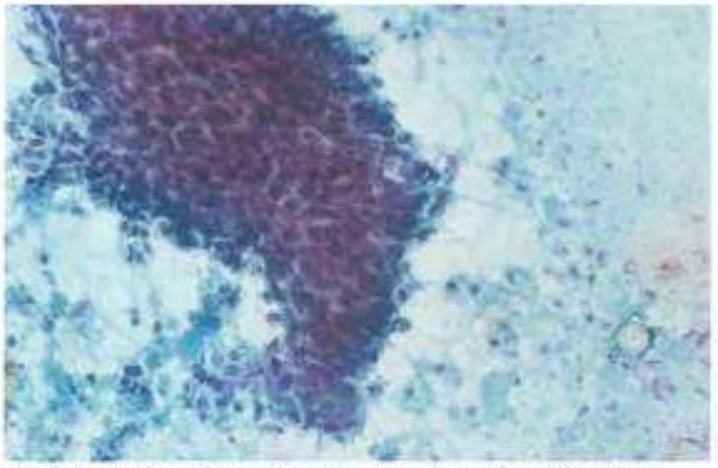


Fig. 10.103 Cytological diagnosis of basal cell carcinoma. Clumps of malignant basaloid cells are present (x40). (Courtesy of Dr Marie Driver.)

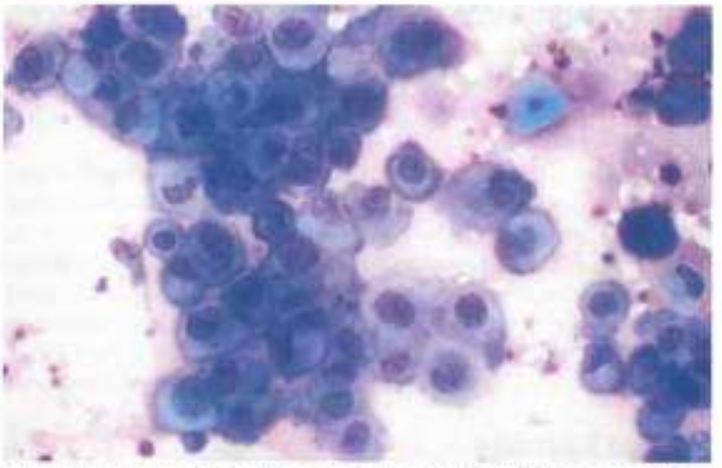


Fig. 10.104 Fine needle aspiration of a lymph node. This shows metastatic squamous cell carcinoma. There are a large number of keratinized squamous cells. Some have large vesicular nuclei and prominent nucleoli.

Management of solar-induced skin cancers

Diagnosis is often the initial problem so that it is appropriate to refer the patient to a dermatologist, who has facilities for immediate biopsy or exfoliative cytology. The latter is a simple and efficient technique. The lesion is scraped with a sharp scalpel blade and the cells, which are so removed, are smeared onto a slide and fixed in a similar way to those of a cervical smear. Clumps of malignant basal cells can easily be identified after appropriate staining (Fig. 10.103). The dermatologist also has the expertise in the use of liquid nitrogen, curettage, photo-dynamic therapy, immunotherapy and 5-fluorouracil and usually holds a joint clinic with a radiotherapist and a dermatological surgeon. A pathologist is often available for fine needle aspiration of involved lymph nodes (Fig. 10.104). Patients who have had a malignancy of the skin should be followed for life because new lesions are common. This is probably best done by the dermatologist. Advice regarding photoprotection and the appropriate use of sunscreens with a high protection factor may prevent further damage.

There are a number of effective remedies. The choice depends on the size, site and nature of the lesion and the physical condition of the patient.

Cryotherapy

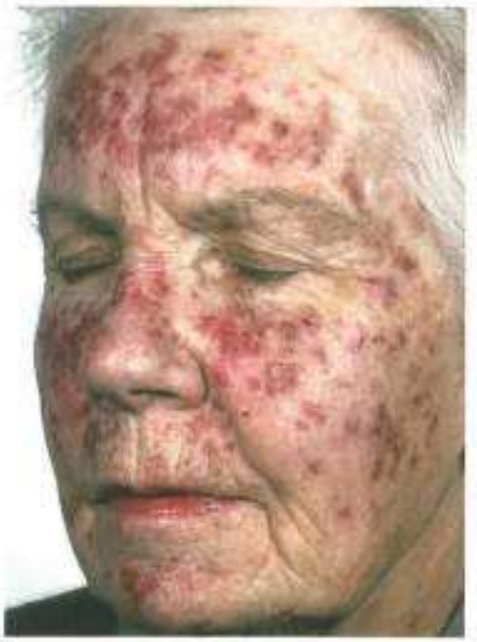
Liquid nitrogen or its equivalent is effective. Only a minor degree of inflammation without blistering is required. It is used principally to treat solar keratoses, either applied with a cotton wool bud or cryojet. Liquid nitrogen cryoprobes are used by some dermatologists for basal cell carcinomas. However, it is fairly unpleasant, probably has no great advantage over other techniques and should only be used for uncomplicated tumours.

Topical therapy

- **5-fluorouracil**

It was first noticed in South Africa, during the treatment of lung cancer with systemic 5-fluorouracil, that solar keratoses in these patients became red and inflamed and then disappeared. The drug was then used topically and found to be effective; it is an antimetabolite that blocks the incorporation of thymidine into DNA. It is particularly suitable for multiple lesions, especially on the face. It is less effective on the hands and forearms, possibly because penetration into the skin is not so good, although combination with topical retinoic acid improves this penetration.

The application of 5-fluorouracil twice daily results in an intense inflammatory reaction (Figs 10.105 and 10.106), which can be disquietening.



Figs 10.105 Solar keratoses treated with 5-fluorouracil cream. An intense inflammatory reaction is produced and detailed explanation of the treatment is required. It is wisest to treat one area at a time.

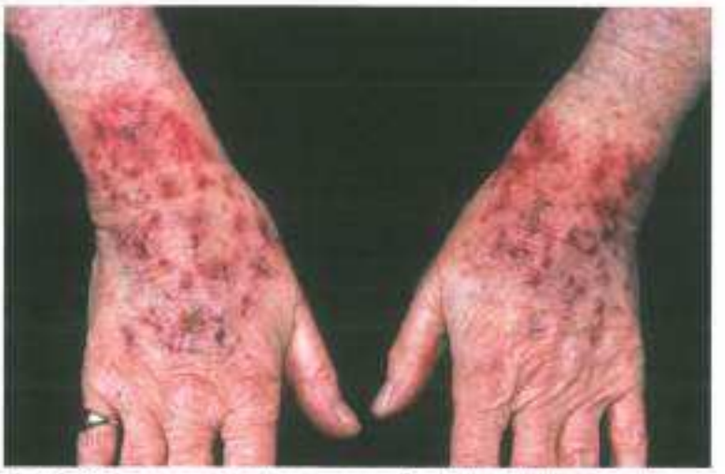
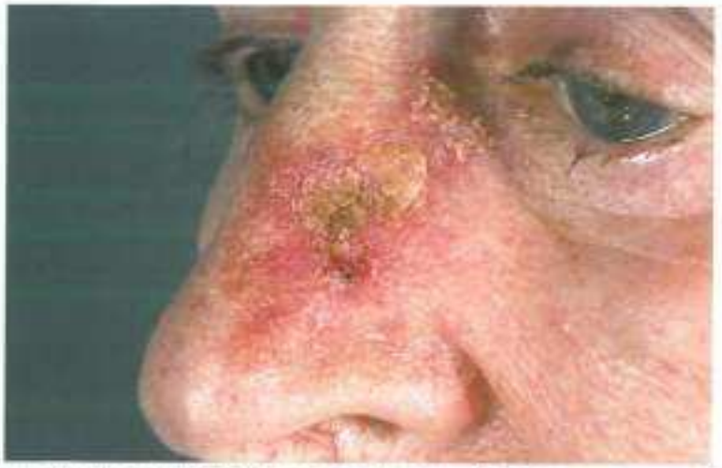
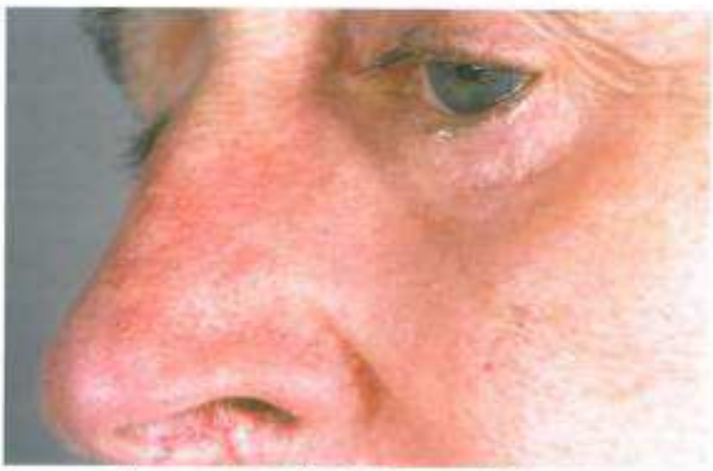


Fig. 10.106 Treatment of solar keratoses. The backs of the hands are less responsive to 5-fluorouracil but the addition of topical retinoic acid enhances its efficacy.





Figs 10.107 and 10.108 Solar keratoses treated with 5-fluorouracil cream. The biopsy-proven plaque was treated effectively. (Courtesy of St Mary's Hospital.)

Careful explanation of its effects is, therefore, required. The inflammation does not occur immediately but usually appears after about 10 days. It is sometimes useful to employ a stop/start policy of 1 week of active treatment followed by 1 week of rest, for a total of 4 weeks of active treatment. The drug has no effect on normal skin, and a major advantage in severely sun-damaged skin is that it destroys the earliest microscopically abnormal cells before they have given rise to macroscopically obvious skin changes. It also stimulates wound healing and dermal remodelling and produces excellent cosmetic results (Figs 10.107–10.110). It is still used systematically for colorectal, pancreatic and head and neck cancer. Other cutaneous side-effects include photosensitivity, erythema, pigmentation, alopecia and nail changes.

- **Imiquimod**

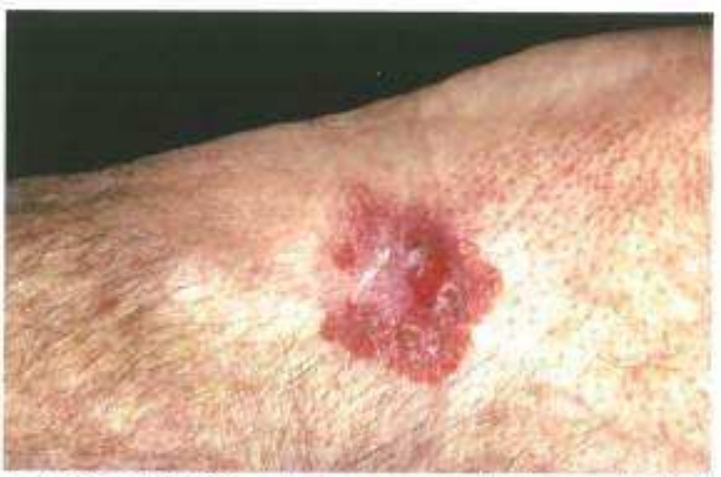
5% Imiquimod topically 2–3 times a week for a month may be effective. It enhances the local immune response against dysplastic cells by producing interferon α, tumour necrosis factor α and interleukin 12 with a resulting cytokine response which may induce or support Langerhans' cell migration and a cytotoxic T cell response. It may also act via Toll-like receptors to stimulate rapid synthesis and release of cytokines from monocytes and macrophages and induce apoptosis.

Both are effective for solar keratoses. 5-fluorouracil has a long-established track record in the management of intraepidermal carcinoma. It does have an effect in superficial basal cell carcinomas but recurrence rates are significant.

Imiquimod is showing promise in the management of lentigo maligna where successful surgery is not feasible.

Photodynamic therapy

Photodynamic therapy involves the topical application of a photosensitizer followed by exposure to red light from either a coherent (e.g. argon-pumped dye laser at 630 nm) or a non-coherent source. This generates highly reactive toxic oxygen intermediates, which promote cell killing. Exogenous δ-alanine bypasses the negative feedback control exerted by haem and δ-alanine synthetase, leading to the production and accumulation of the intermediate metabolite protoporphyrin IX, which is a potent endogenous 'photosensitizer' in epidermal cells and pilosebaceous units. It produces excellent results on the face and scalp but less so on the limbs and trunk and is not effective for hyperkeratotic solar keratoses. It may be very effective for superficial basal cell carcinomas but patients need to be followed up because recurrences occur. It is a painful experience.



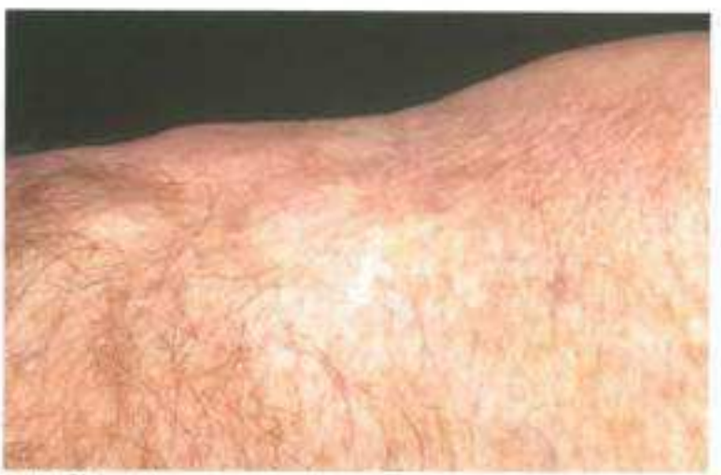


Fig. 10.109 and 10.110 Bowen's disease treated with 5-fluorouracil. This lesion (Fig. 10.109) would have required a skin graft if excised surgically. It was successfully treated with 5-fluorouracil, with no recurrence 6 years later (Fig. 10.110).

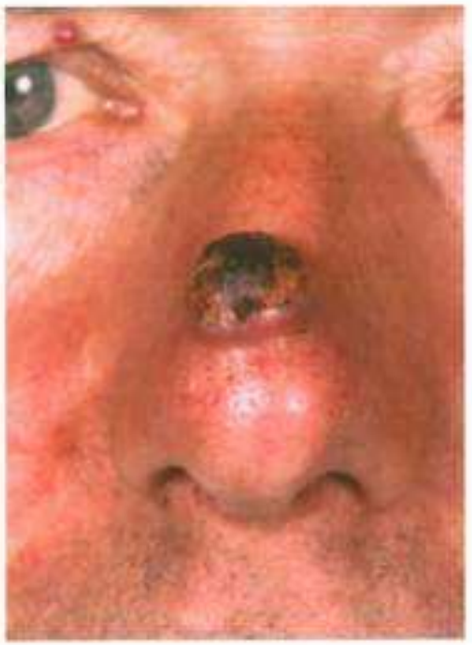


Fig. 10.111
Keratoacanthoma.
This well-defined raised nodule with a keratin centre had erupted rapidly over a 4-week period.

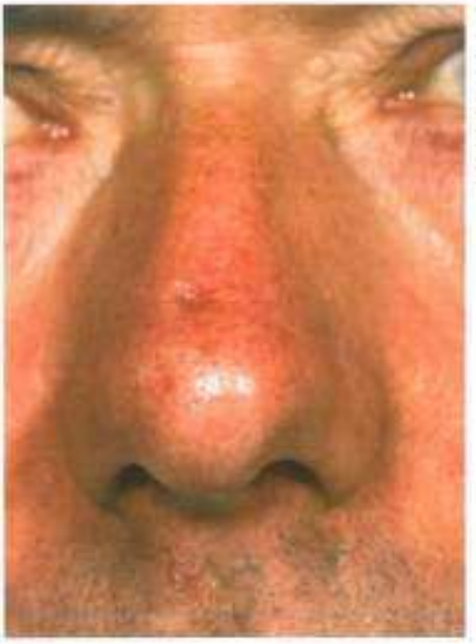


Fig. 10.112
Keratoacanthoma.
The lesion (Fig. 10.111) was removed by curettage and cautery. The result 4 weeks later is shown.

Curettage and cautery

Curettage and cautery is the most common technique used by the dermatologist. It is suitable for small papular basal cell carcinomas less than 1 cm in diameter and superficial basal cell carcinomas. The tumour mass is soft and friable and comes away easily when scraped with the curette. The surrounding fibrous stroma is more resistant and should be cauterized and then scraped away again. Healing occurs within 3 weeks, with surprisingly little scarring; as a result, this is an effective therapy in experienced hands. It is very simple and can be done quickly under local anaesthesia at the time of the consultation. This technique is usually contraindicated for:

- lesions greater than 1 cm in diameter
- lesions around the eyes, nostrils and ears
- deeply ulcerated lesions
- morphoeic basal cell carcinomas.

It is also used for hypertrophic actinic keratoses and Bowen's and is very useful for keratoacanthomas, particularly on the face (Figs 10.111 and 10.112), where site constraints make primary surgical excision more complex. It may be used in carefully selected cases of early well-differentiated squamous cell carcinomas. In general, it is not used for actinic keratoses because cryotherapy and topical agents are effective but it does have the advantage of providing tissue for histological examination.

Surgery

This is the preferred option for basal and squamous cell carcinomas and the only option for malignant melanoma. It is the treatment of choice for:

- lesions around the eye, nose and ear
- morphoeic basal cell carcinomas
- recurrence after radiotherapy
- younger individuals.

The dermatological surgeon has the skills to excise adequately and to repair, either primarily or with a graft or rotation flap. The success of the operation, that is adequate clearance, can be confirmed by the pathologist.

Mohs' chemosurgery

Mohs' chemosurgery is limited to specialized centres, although it is becoming more commonplace. It is probably the best treatment for extensive invading destructive lesions and surgical failures. The principle of the technique is microscopic control at the time of the removal of the tumour, so special laboratory facilities are required. The undersurface of each layer of excised tissue is examined by frozen section until the margins and base are deemed free of tumour. It is painstaking and, for the majority of patients, is cost/time ineffective.

Mohs' micrographic surgery should be considered for:

- recurrences after surgery or radiotherapy
- high-risk anatomical sites over embryonic fusion planes, cartilage and bone
- certain types of tumour, e.g. morphoeic
- large tumour size
- perineural involvement
- immunosuppressed patients
- need for maximum tissue preservation.

Skin cancers that recur after surgery are able to spread along planes of least resistance, for example previously undermined surgical borders or through scar tissue, and they can be masked under flaps and grafts. The high-risk anatomical sites include the theoretical embryonic fusion planes (the pre- and retroauricular areas, nasolabial folds, inner canthus and philtrum) and tumour overlying cartilage and bone. There is evidence that midfacial tumours do invade more deeply and present more difficulties. Tumours overlying the cartilage of the pinna and tip of the nose and the bone on the scalp, temple, upper nose and forehead may spread laterally along planes of least resistance. Morphoeic, micronodular, field fire (microcentric) and metatypical (basosquamous) tumours are particularly aggressive types. Finger-like extensions may grow deeply and laterally in a dense fibrous stroma, and small strands of tumour cells may extend beyond the apparent clinical margins of the tumour. In the micronodular type, the tumour nests are smaller but more dispersed than the nodular variety; in the field fire type, the pathology is microcentric and discontinuous foci are present. The basosquamous type behaves more like a squamous cell carcinoma. Large size and perineural involvement (particularly with squamous cell carcinomas) are further indications. Tumours in immunosuppressed individuals, which tend to be more aggressive, and anatomical sites where there is the greatest need for maximum tissue preservation (such as may occur on the face, particularly the lip, and in the anogenital region) are other indications for Mohs' chemosurgery.

Mohs' chemosurgery is labour intensive. It requires an experienced pathologist to interpret the on-site frozen section analysis and a trained surgeon and nursing staff. For the patient, it requires time waiting between stages of surgery while the frozen sections are performed and then reconstruction by a plastic surgeon following complete removal of the tumour. However, for the types of tumour outlined above, there is a high cure rate and good tissue conservation.

Radiotherapy

Basal cell and squamous cell carcinomas are radiosensitive. Modern techniques of fractionating the dose have greatly improved the cosmetic results. Previously, single (Fig. 10.113) doses of irradiation resulted in scarring and sometimes radionecrosis. A marked reaction occurs during treatment and subsequently atrophy, scarring, telangiectasia and pigmentary abnormalities (*radiodermatitis*) result. The irradiated epidermis is hyperkeratotic and either acanthotic or atrophic (Fig. 10.114). It may show the features of solar (radiation) keratoses and be the site of origin of basal cell and squamous cell carcinomas. The latter may cause particular diagnostic difficulties as it is often of a poorly-differentiated or anaplastic type. The dermis is typically fibrosed and homogenized (Fig. 10.115); while superficially telangiectatic vessels are the rule, in its deeper aspects endarteritis obliterans is a common feature. Although spindle cell sarcomatous conditions have been reported as a feature of chronic radiation dermatitis, it is more likely that most, if not all, represent spindle cell squamous carcinomas.

Radiotherapy is particularly suitable for:

- the elderly, and the 'timorous'
- large lesions
- surgical failures.

It should, however, be noted that radiotherapy cannot be repeated and should be avoided in:

- **Certain sites** Irradiation of the ear, lower leg and back of the hand may result in radionecrosis. If possible, basal cell carcinomas of the lower eyelid should not be irradiated because this leads to loss of eyelashes, stenosis of the lacrimal duct and epiphora. These may be avoidable with plastic surgery.
- **Certain types**
  - morphoeic basal cell carcinoma is relatively radioresistant and there is no histological proof that it has been eradicated after radiotherapy
  - superficial basal cell carcinoma may be treated with radiotherapy, but it leaves a poor cosmetic result with prominent radiodermatitis (Fig. 10.116); recurrences do occur.

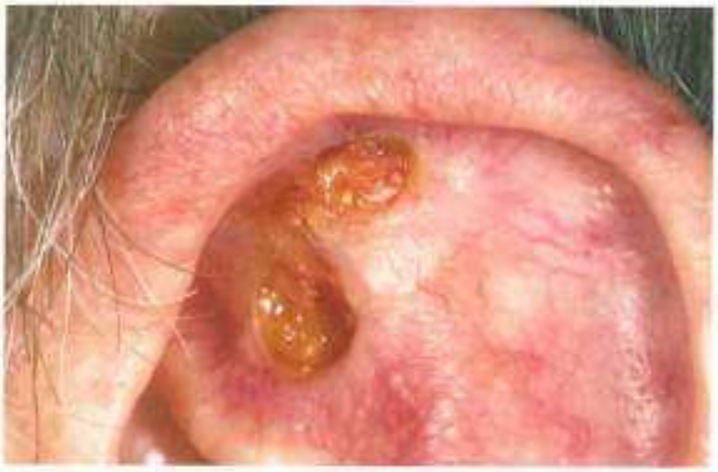


Fig. 10.113 Radionecrosis. Radiotherapy is contraindicated in certain sites if radionecrosis is to be avoided.

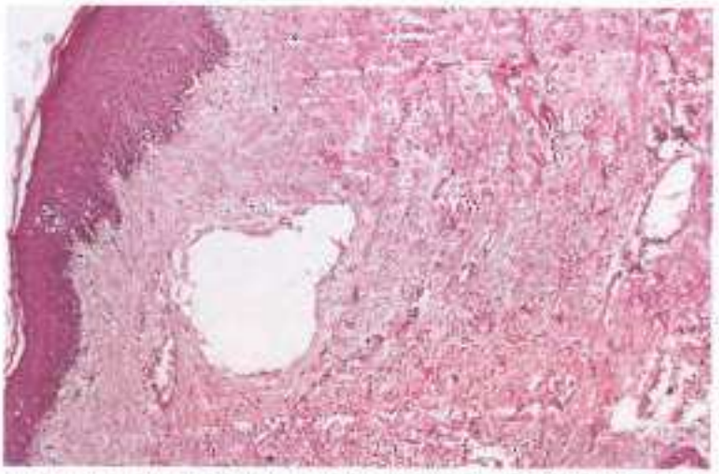


Fig. 10.114 Radiation dermatitis. There is acanthosis. The dermis is fibrosed and contains telangiectatic blood vessels.

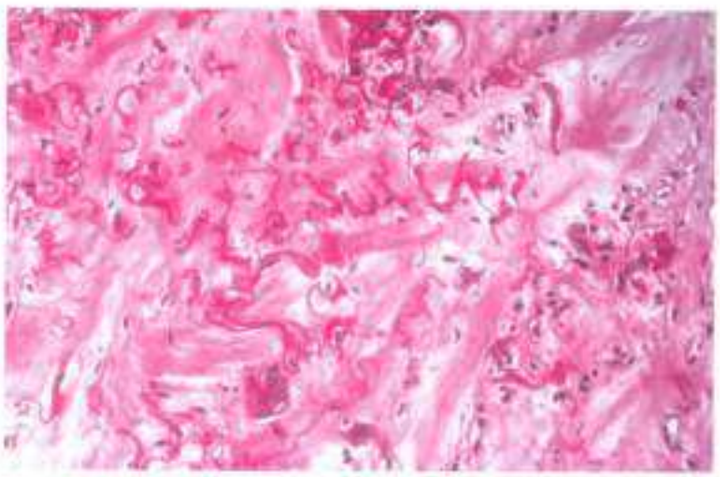


Fig. 10.115 Radiation dermatitis. This field shows dermal fibrosis, elastosis and occasional bizarre postirradiation fibroblasts.

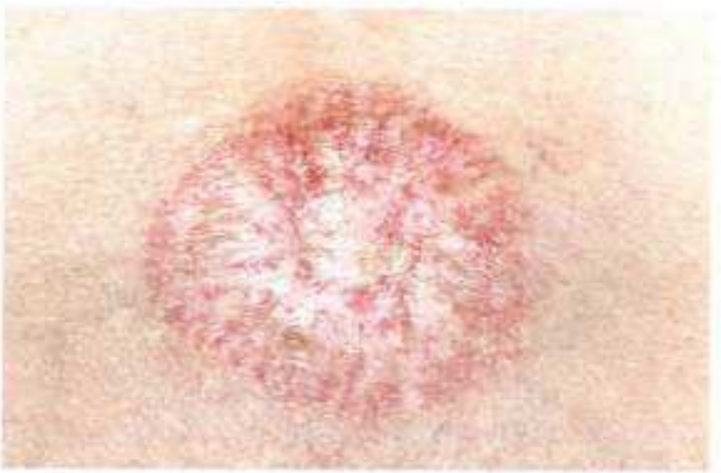


Fig. 10.116 Radiodermatitis. Irradiation of the skin results in atrophy, scarring and telangiectasia.

Prevention (Solar protection and sunscreens)

Sunburn is caused by UVB (290–320 nm) and is preventable with modern sunscreens. There is good evidence that a factor 30 screen will reduce the number of observable sunburn cells more than a lower factor. Studies have also shown that regular use of sunscreens reduces the occurrence of further actinic keratoses compared with those who do not use them. Tanning is caused by UVA (320–400 nm) and is not so easily prevented. Avobenzones and octocrylenes afford some protection. Zinc oxide and titanium dioxide lose their efficacy in the UVA 1 range. In general, tinted physical screens are superior to chemical screens, which may occasionally cause contact dermatitis. Some have raised concerns that so-called sunblocks are deceptive. Users believe themselves to be protected and because they do not burn, they may receive more UVA irradiation than they otherwise would if they were not using one, therefore doing more damage to the skin. Certainly, sun avoidance and protective clothing (including hats) remain the best approach.

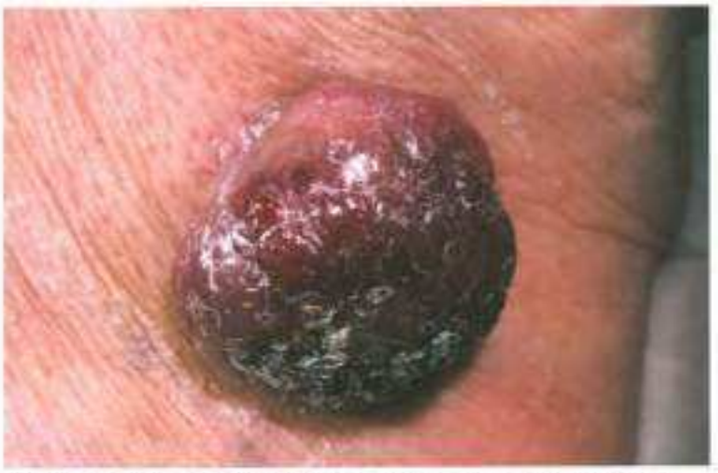


Fig. 10.117 Merkel cell tumour. There is a red eroded crusted nodule on the limb. Metastasis to locoregional lymph nodes usually occurs within 8 months if untreated.

Merkel cell tumour

A rare, highly aggressive neuroendocrine skin tumour of the elderly and immunosuppressed.

Aetiology

First described by Toker in 1972 as a trabecular carcinoma of the skin, ultrastructural studies revealed that the Merkel cell tumour contained neurosecretory granules similar to those in Merkel cells. These cells are part of the APUD system (amine precursor uptake and decarboxylase system) and, although theoretically considered to be cells of neural crest origin that migrate to various sites during embryogenesis, they probably develop from epithelial precursor cells in various sites since many have squamous or eccrine differentiation and the epithelial marker BER-EP4 is positive. Merkel cells are clear cells of the basal cell layer of the epidermis closely related to nerve fibres. They were described by Merkel after staining the skin of the nose of a mole with osmium tetroxide. They function as an end organ for touch sensation. They are ubiquitous but are especially found around the neck, abdomen, gingiva and palate. Merkel cell tumour is most common in the elderly, secondary to chronic solar exposure and immunosuppression (drugs and chronic lymphatic leukaemia). A Merkel cell polyomavirus (a new virus belonging to the polyomaviridae family) has been identified in tumour tissue.

Clinical Features

Symptoms

An asymptomatic lump on the skin (Fig. 10.117), which expands rapidly.

Morphology

A painless subcutaneous nodule often with a red or bluish hue.

Distribution

Anywhere on the body but particularly on the face, neck and limbs.

Histopathology

The lesion has a trabecular pattern with sheets of tumour cells with large vesicular nuclei and tiny nucleoli, often with a mixture of cells with smaller hyperchromatic nuclei (Figs 10.118 and 10.119). Mitoses are prominent. Cytokeratin 20 is the most useful stain for differentiating from other small cell tumours such as lung cancer. CAM 5.2, an antibody which reacts with low molecular weight cytokeratins and neurofilaments, is also helpful.

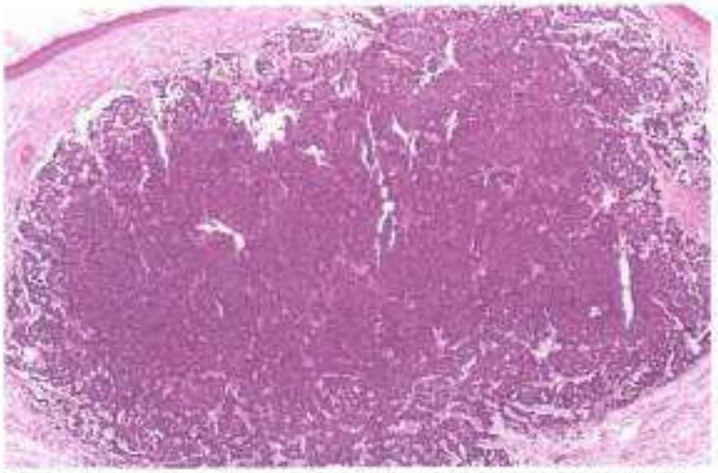


Fig. 10.118 Merkel cell tumour. There is extensive infiltration of the dermis by the tumour.

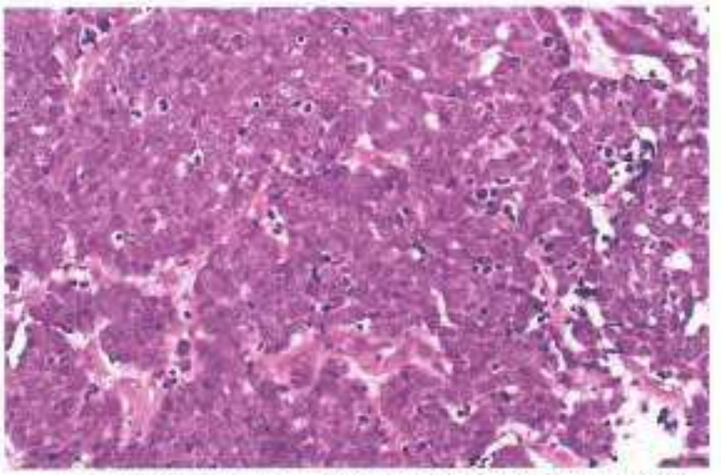


Fig. 10.119 Merkel cell tumour. The tumour nuclei are large, pale staining and contain tiny nucleoli.

Management
The prognosis in Merkel cell tumour is related to the cell size. Small cells with scant cytoplasm, little epithelial differentiation and a high mitotic rate indicate a poor prognosis. Large tumours and lesions on the buttocks, thigh or trunk have a worse prognosis than those on the distal extremity. The lesion is aggressive and commonly recurs after surgery. It invades subcutaneous tissue and spreads via cutaneous and deep lymphatics to the lymph nodes and metastasizes to the skin, bone, brain, orbit and retroperitoneum. Wide excision, Mohs' micrographic surgery possibly with block dissection of the lymph nodes, if sentinel node biopsy is positive, and adjuvant radiotherapy are the treatments of choice. Chemotherapy is not effective although imatinib has been tried since the proto-oncogene C-Kit is expressed by Merkel cells.

Sebaceous carcinoma
A locally invasive malignant tumour with sebaceous epithelial differentiation; it rarely metastasizes.

Aetiology
Sebaceous carcinoma is uncommon but may be associated with the Torre–Muir syndrome, arsenic ingestion and previous radiotherapy.

Clinical Features
Symptoms
A fairly slow growing lesion on the skin.

Morphology
A yellow or orange (sometimes) verrucose plaque or nodule (Fig. 10.120).

Distribution
Anywhere, but particularly on face and scalp and around the eye.

Histopathology
There are numerous lobules of sebaceous glands at various stages of maturity replacing the epithelium (Fig. 10.121).

Management
A sebaceous carcinoma should be completely excised.

Microcystic adnexal carcinoma
A rare slow-growing tumour of the face, derived from sweat glands.

Aetiology
Eccrine gland carcinomas are rare. They may arise in a pre-existing benign lesion, such as an eccrine poroma, or may be malignant from the start. They include an adenocarcinoma of the sweat gland and microcystic adnexal carcinoma. Although the latter is uncommon, it occurs on the face and may be misdiagnosed unless a biopsy is done; it requires prompt attention because it has a tendency for perineural spread and local recurrence is common and the lesion may be painful.

Clinical Features
Symptoms
An asymptomatic or painful plaque (Fig. 10.122).

Morphology
Often quite inconspicuous because it is only just elevated as a plaque.

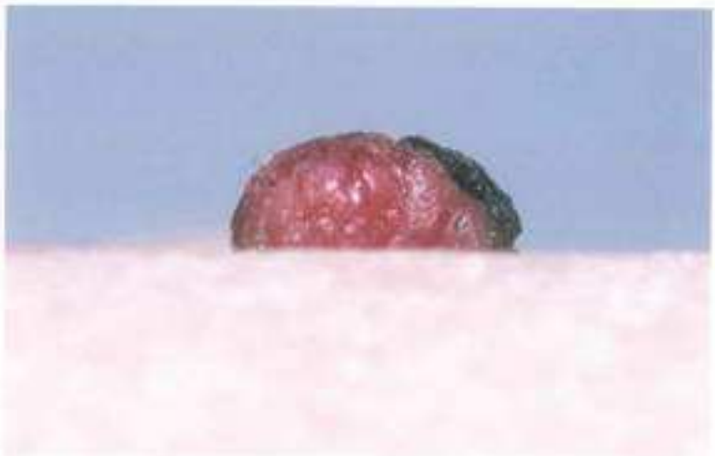


Fig. 10.120 Sebaceous carcinoma. A well-circumscribed red/orange nodule is present. Sebaceous carcinomas are associated with the Torre–Muir syndrome.

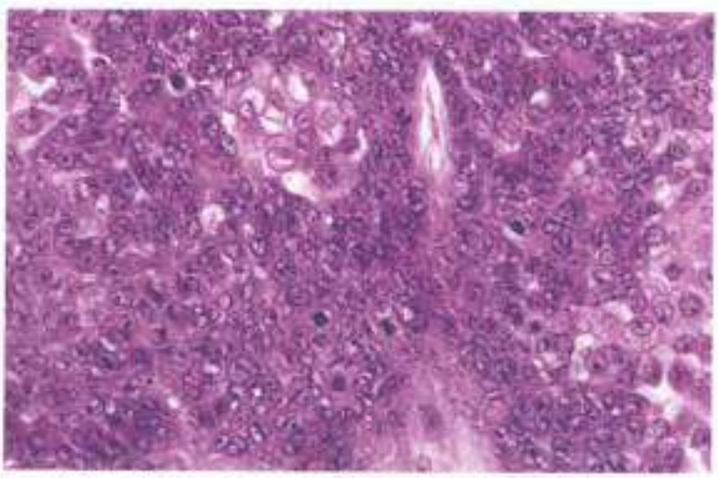


Fig. 10.121 Sebaceous carcinoma. There is focal continuity with the epidermis and an irregular growth pattern. Basophilic germinative cells predominate and keratocysts are present.

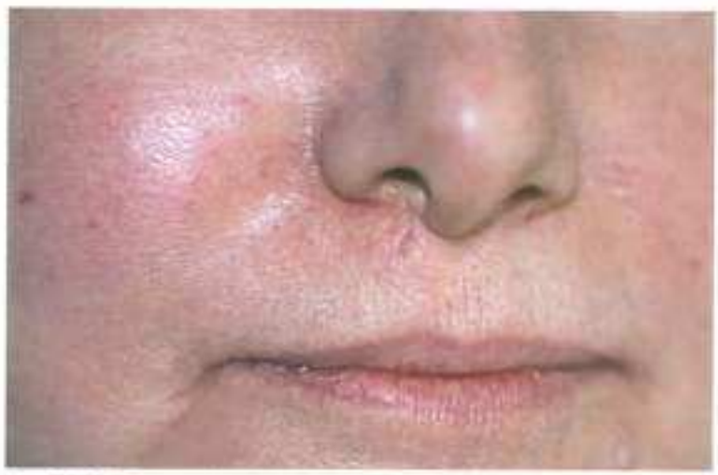


Fig. 10.122 Microcystic adnexal carcinoma. A red and ivory white plaque is present in and around the patient's right nostril. The diagnosis is unlikely to be made until a biopsy has been performed.

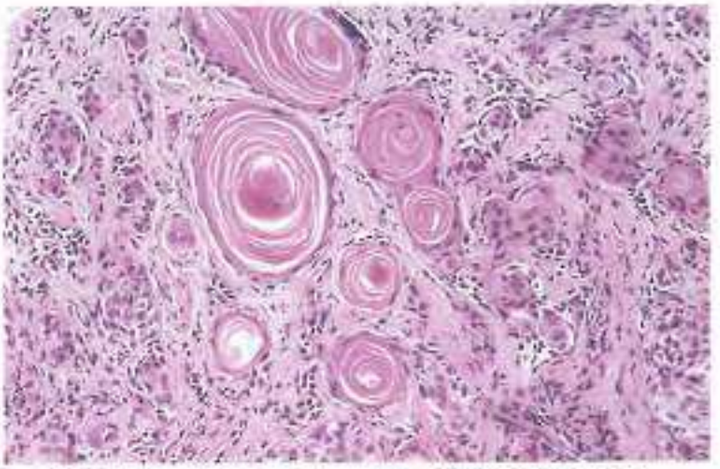


Fig. 10.123 Microcystic adnexal carcinoma. There are narrow epithelial strands of tumour and small ductules, in deeper sections of the lesion, which may not be seen if the biopsy is too superficial.

Distribution
Particularly on the upper lip.

Histopathology
A deep biopsy is necessary because there are cords of keratinocytes, many showing ductular lumina (Fig. 10.123), associated with numerous small or larger squamous microcysts in a dense scirrhous fibrous stroma superficially with strands of epithelial tumour cells only seen more deeply. Perineural invasion is frequently observed.

Management
Mohs' chemosurgery is ideal because microcystic adnexal carcinoma tends to recur otherwise.

Dermatofibrosarcoma protuberans

A locally malignant dermal tumour of fibroblasts.

Aetiology
Although a tumour of unknown aetiology, occurring in both sexes in middle years, cytogenetic abnormalities such as t(17:22) translocations and supernumerary ring chromosomes derived from chromosome 22 are present and result in fusion sequences of COL1A1 and PDGF β genes.

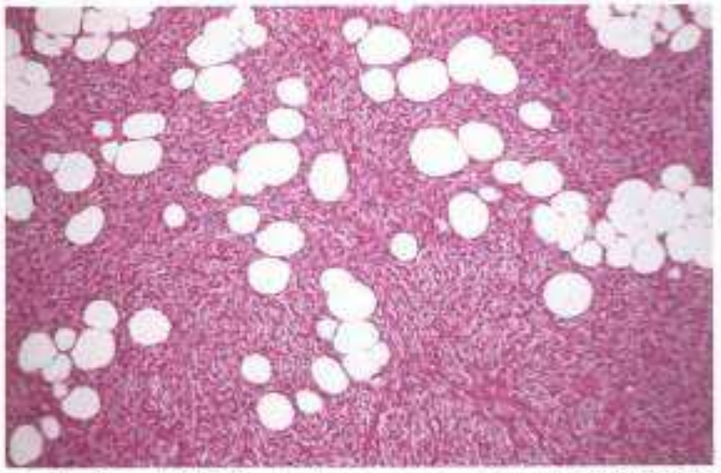
Clinical Features
Symptoms
Usually painless but it may become uncomfortable as it enlarges.

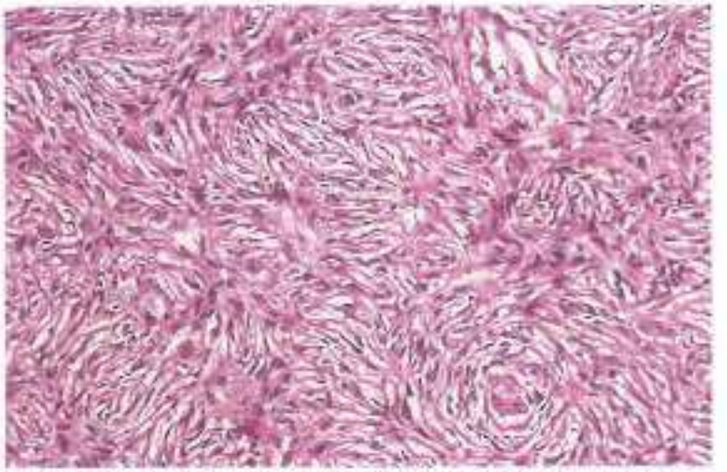
Morphology
Slow-growing, fibrous plaques, papules or dermal nodules coalesce and change from a flesh colour to a blue or red discoloration (Fig. 10.124). There is occult pseudopodal infiltration of adjacent soft tissues. Clinical variants simulate morphoea, atrophoderma and angiomas. It is often mistaken for a keloid or dermatofibroma.

Fig. 10.124 Dermatofibrosarcoma protuberans. There is a multinodular mass arising from a pigmented plaque. The shoulder is a classic site.

Distribution
The back and front of the trunk are common sites.

Histopathology
It is composed almost entirely of uniform spindle cells with vesicular nuclei that show little or no pleomorphism and scanty eosinophilic





Figs 10.125 and 10.126 Dermatofibrosarcoma protuberans. This spindle cell tumour of probable fibroblastic histogenesis typically infiltrates the subcutaneous fat (Fig. 10.125) and characteristically displays a storiform pattern (Fig. 10.126).

cytoplasm. Mitoses are frequently conspicuous. The cells are arranged in a uniform storiform pattern. The tumour is present largely in the dermis but typically infiltrates the subcutaneous tissues (Figs 10.125 and 10.126). It is CD34 positive but negative for smooth muscle actin, desmin and S100.

Management

It rarely metastasizes, but is locally malignant and recurrences are the rule if the lesion is not widely excised. It is often best managed by Mohs' surgery. Imatinib is an adenosine triphosphate analogue, which inhibits the adenosine triphosphate binding site of platelet-derived growth factor β receptor tyrosine kinase of dermatofibrosarcoma protuberans and may prove to be of benefit.

Cutaneous angiosarcoma

A rare aggressive malignant tumour of vascular origin, affecting the head and neck.

Aetiology

Terminology is confusing. Cutaneous angiosarcoma (syn. malignant haemangioendothelioma) is an aggressive tumour. *Epithelioid haemangioendothelioma* is a rare vascular tumour characterized by an epithelioid endothelial cell proliferation, which is of intermediate malignant potential, most arising in deep soft tissues but sometimes with adjacent cutaneous involvement and rarely in the skin itself. *Malignant haemangioendotheliomatosis* is now recognized as an intravascular B cell lymphoma. An angiosarcoma may develop in a lymphoedematous limb, particularly following mastectomy. The syndrome was originally described in the ipsilateral lymphoedematous arm following mastectomy (Stewart–Treves syndrome) and this is still the most common cause. However, the condition has been reported in lymphoedema secondary to other mechanisms, such as axillary node dissection for metastatic melanoma, of the abdominal wall following lymph node dissection in association with carcinoma of the penis, and in other causes of lymphoedema including filaria and idiopathic lymphoedema. The risk of developing angiosarcoma following mastectomy is about 0.5% within 5 years. The histopathological features are similar to those of angiosarcoma of the scalp and face. The prognosis is poor and amputation has to be considered.

The cause of cutaneous angiosarcoma is unknown. It occurs in the elderly, particularly males.

Clinical Features

Symptoms

An asymptomatic bruise-like lesion initially which is often not noticed because it occurs in the scalp until it ulcerates and bleeds.

Morphology

There is a livid red or purple plaque (Fig. 10.127).

Distribution

Cutaneous angiosarcomas occur on the scalp extending onto the forehead or it may begin around the eyes with a slight degree of oedema and minimal erythema, almost like a 'bruise' (Fig. 10.128).

Histopathology

Cutaneous angiosarcomas are composed of anastomosing vascular channels lined by pleomorphic and hyperchromatic endothelial cells. Mitotic figures are often present. In less-well-differentiated examples, the tumour cells often infiltrate (dissect) the dermal collagen bundles. Poorly differentiated angiosarcoma is often of a spindle cell type and is frequently a source of diagnostic difficulty (Fig. 10.129).

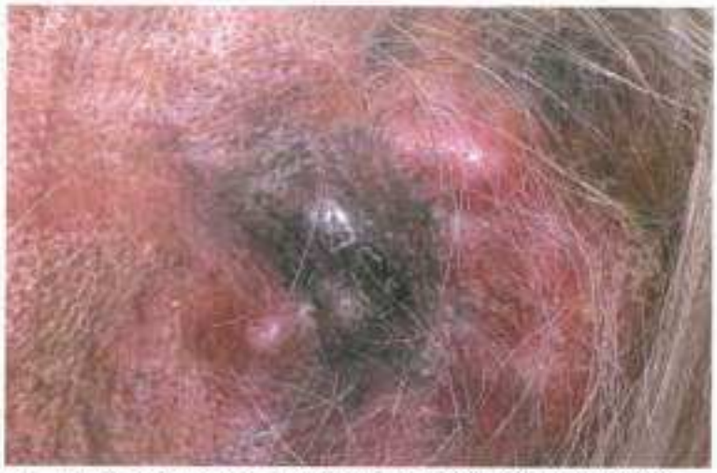


Fig. 10.127 Angiosarcoma. There is a livid red or purple plaque, which often starts in the scalp and is not noticed until it encroaches onto the forehead.

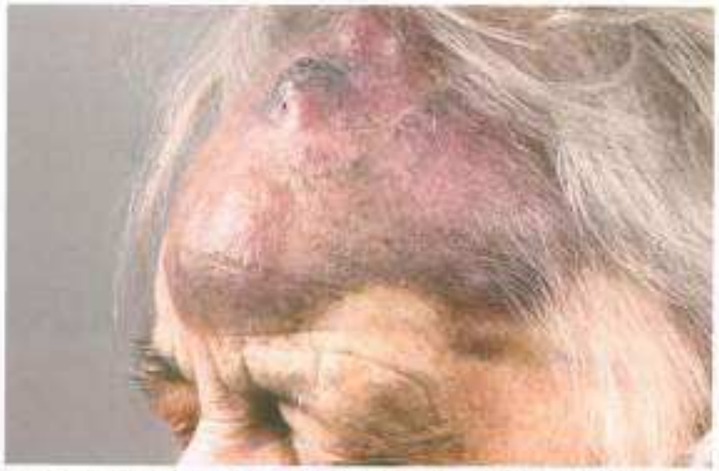


Fig. 10.128 Cutaneous angiosarcoma. This is an aggressive tumour in the elderly. The whole scalp and forehead is involved with a diffuse purple nodular tumour.

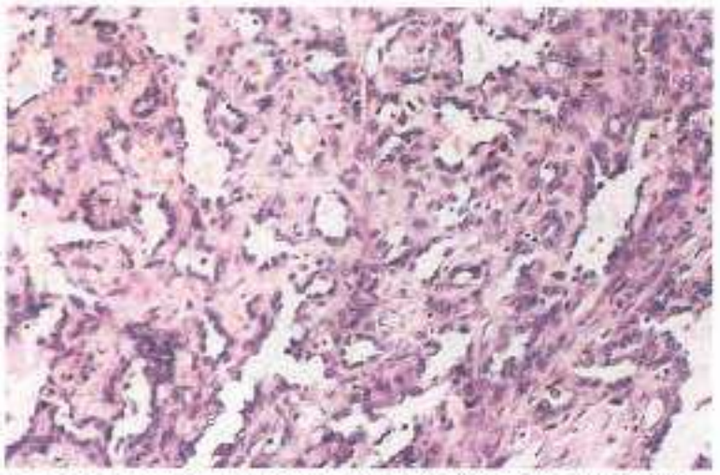


Fig. 10.129 Cutaneous angiosarcoma. Vascular differentiation is clearly seen. Note the pleomorphism of the endothelial cells.

Management

By the time of presentation, a cutaneous angiosarcoma is usually too advanced for surgery. Most cases appear to be multifocal and the lesion extends beyond what is clinically apparent. The prognosis is poor, with metastases to the cervical lymph nodes and subsequently to the viscera and skeleton. Better survival figures have been reported in small lesions. Wide-field electron beam therapy, liposomal doxorubicin and thalidomide are also used.

Kaposi's sarcoma

Kaposi's sarcoma is a malignant cutaneous vascular proliferation occurring in several different clinical contexts.

Aetiology

There are four subgroups of Kaposi's sarcoma.

- **Classic** First described in 1872, this occurs in the elderly, particularly males, of Mediterranean or Eastern European Jewish ancestry.
- **African endemic** This is an endemic disorder of equatorial Africa, occurring in the same geographical areas as Burkitt's lymphoma, particularly Uganda. It is much more common in Africans than in Europeans living in the area. There are four forms of the disease: (i) a generally benign nodular group, which is similar to classic Kaposi's sarcoma, (ii) a more florid type, (iii) an infiltrative type, and (iv) a fulminant lymphadenopathic variety seen in children. The skin is rarely involved in the latter type and it is usually fatal within 3 years.
- **Immunosuppression associated** This iatrogenic variety occurs with immunosuppressive therapy for organ transplantation (particularly renal), lymphomas and autoimmune disorders. On the whole, the lesions are localized to the skin and visceral involvement is infrequent although this form is more aggressive than the classic type. The lesions are usually, but not always, reversible on changing or discontinuing the immunosuppressive therapy.
- **AIDS associated** This was most common in homosexual males, rare in haemophiliacs treated with contaminated blood products and only occurred in females infected by a bisexual man. It was particularly common in San Francisco, Los Angeles and New York but due to early diagnosis and treatment is now uncommon. It tends to develop once the $CD4^+$ cell count has dropped below 500×10^6 cells/l, and 50% of the patients have lymphadenopathy in association with the skin lesions.

There is no fundamental histopathological difference between the various types. Human herpesvirus 8 (HHV-8) has been found in all forms of Kaposi's sarcoma and is now known by some groups as KSHV (Kaposi's sarcoma herpesvirus). It shows tropism for flat endothelial cells lining the vascular spaces and the spindle cells of Kaposi's sarcoma; although it is also found in association with B cell body cavity lymphomas (primary effusion lymphoma) and Castleman's disease, the case for HHV-8 being the infectious cause is very strong.

Clinical Features of Classic Kaposi's Sarcoma

Symptoms

Red or purple blotches on the extremities.

Morphology

The blue/red macules of classic Kaposi's sarcoma become a deeper purple colour as they develop into plaques (Figs 10.130 and 10.131) and nodules. They spread in a centripetal manner. There is unilateral and subsequently bilateral oedema. Postinflammatory hyperpigmentation is common.

Distribution

The lesions of classic Kaposi's sarcoma begin on the ankles and lower limbs and subsequently spread to the hands, ears and nose. The mucous membranes and viscera may be involved, including the gastrointestinal tract, liver, lungs, kidneys, lymph nodes and spleen.

Clinical Features of AIDS-associated Kaposi's

Symptoms

Asymptomatic purple blotches on the skin.

Morphology

The lesions are pink, purple or brown in colour; they initially start as patches and become more infiltrated as plaques, papules or nodules.

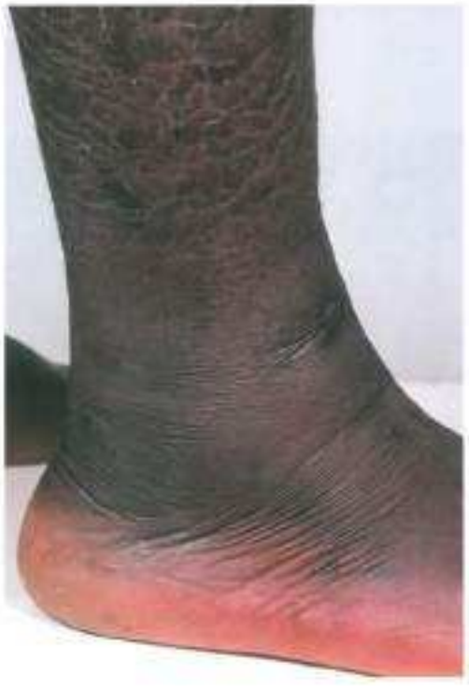


Fig. 10.130 Kaposi's sarcoma. There is oedema and a number of pigmented plaques. This is the variety seen in black-skinned Africans associated with HIV infection.

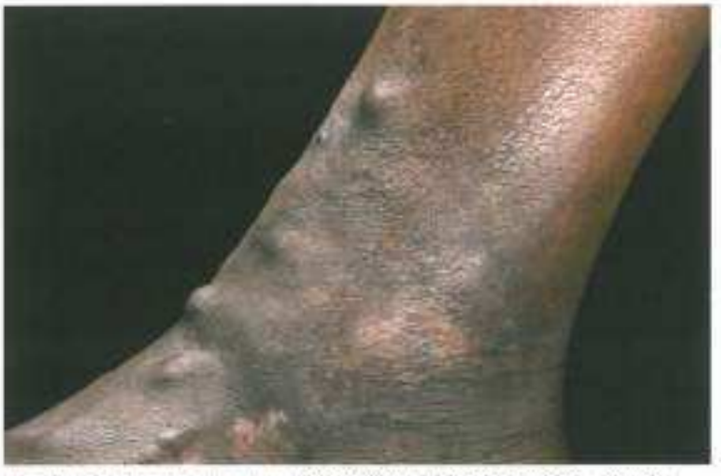


Fig. 10.131 Kaposi's sarcoma. In the African HIV-associated form, nodules develop from plaques on the lower legs associated with oedema.

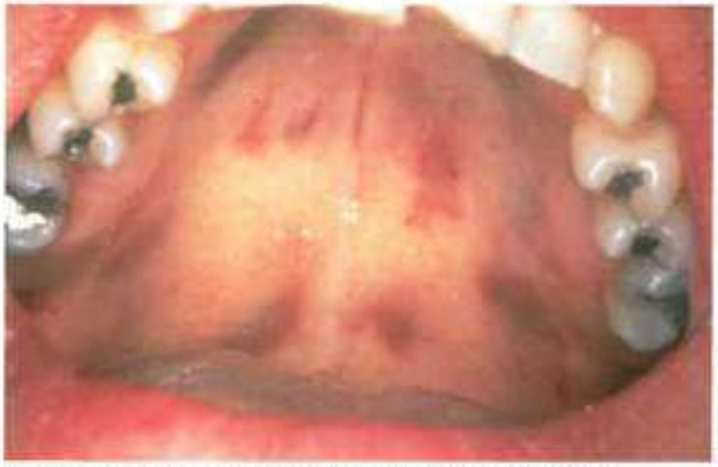


Fig. 10.132 Kaposi's sarcoma. The hard palate is frequently affected.

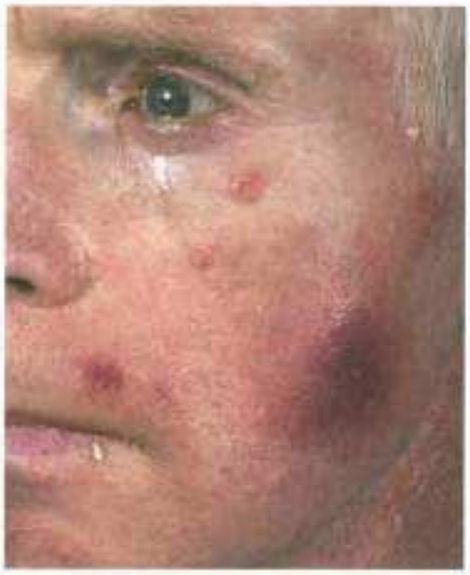


Fig. 10.133 Kaposi's sarcoma. This is no longer common because of early diagnosis and treatment; plum-coloured papules, plaques and nodules are characteristic on the face in human immunodeficiency virus infection.

Distribution

Anywhere on the skin or mucous membranes (Fig. 10.132) but particularly on the face (Fig. 10.133), on the nose (Fig. 10.134) and around the back of the ear (Fig. 10.135) and earlobes. It may also occur on the penis, trunk, legs and feet (Fig. 10.136). It may occur around the eyes and become quite exophytic, ulcerated and colonized with pseudomonas. The acral lesions may become hyperkeratotic, almost like psoriasis. Once there is lymphatic involvement, the skin has a *peau d'orange* appearance, with oedema of the legs, genitalia and groin. About 20% have involvement of the viscera, particularly the gastrointestinal tract, liver, spleen, bone marrow, urogenital tract, pharynx and heart.

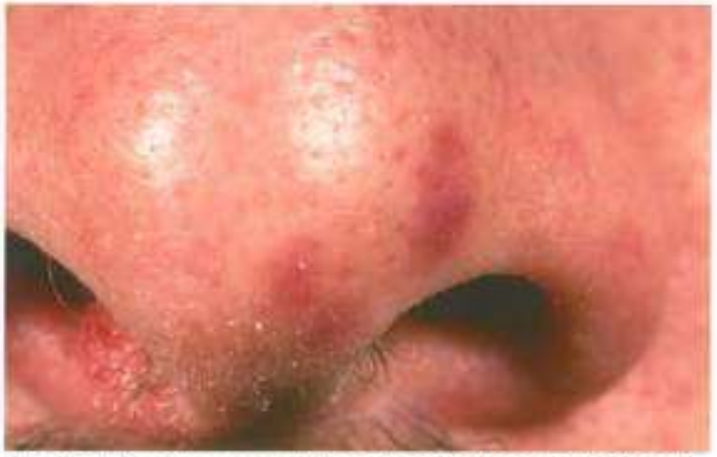


Fig. 10.134 Kaposi's sarcoma. The papules commonly occur on the face and are a distressing stigma of the disease.

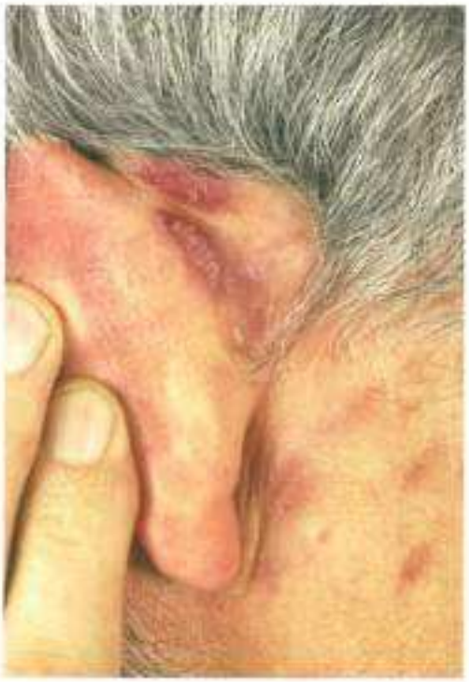


Fig. 10.135 Kaposi's sarcoma. Purple macules and papules are present behind the ear.

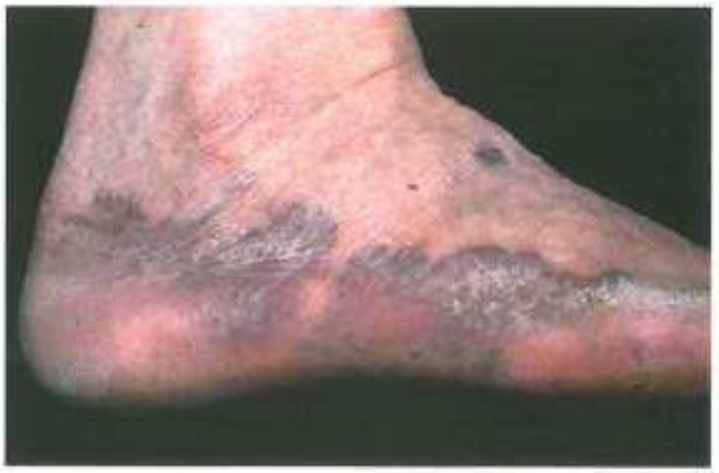


Fig. 10.136 Kaposi's sarcoma. Purple plaques and nodules occur on the feet and legs. Oedema follows. (Courtesy of the late Dr Neil Smith.)

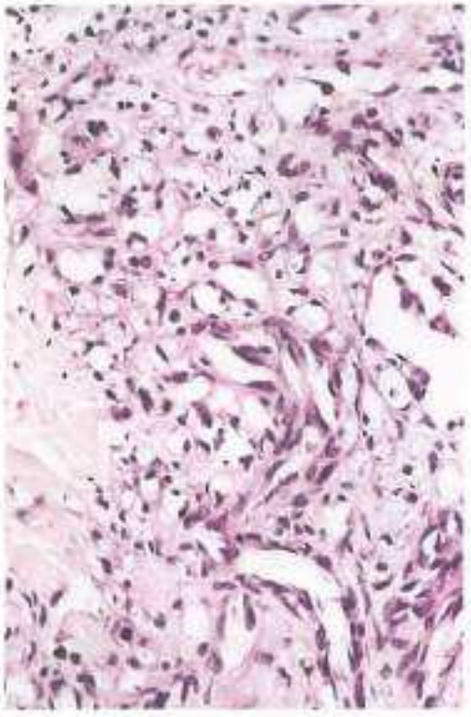


Fig. 10.137 Kaposi's sarcoma. The early stages are characterized by the development of irregular cleft-like vascular channels lined by plump, slightly atypical and hyperchromatic endothelial cells.

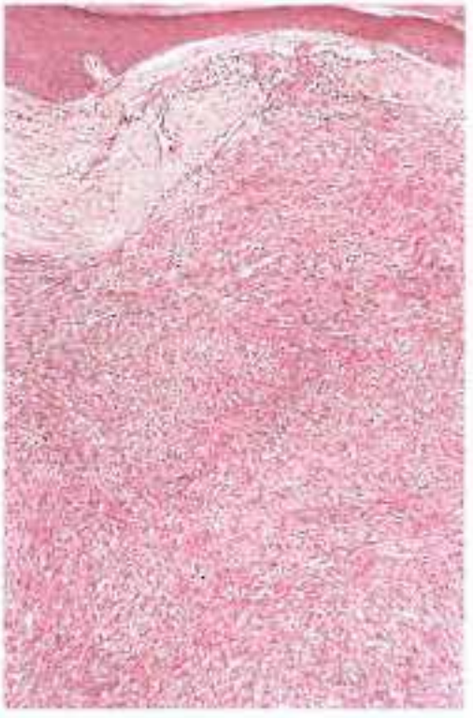


Fig. 10.138 Kaposi's sarcoma. The appearances of this established tuberous nodule are characteristic. Note the interlacing fascicles of spindle cells and the conspicuous red blood cell component.

Histopathology

Kaposi's sarcoma develops from the endothelial cells that line the lymphatics and blood vessels of the skin and visceral organs. There is vascular and spindle cell proliferation, endothelial atypia (Fig. 10.137) and haemosiderin deposition. In established disease, the tumour consists of plump eosinophilic spindle cells, often separated by erythrocytes (Fig. 10.138). It may be a reactive rather than a true neoplastic disorder. It does not produce conventional metastases but tends to spread in a rather multifocal way. Stains for HHV-8 are positive.

Management

Individual lesions of Kaposi's sarcoma may be excised or treated with cryotherapy or lasers. Intralesional cytotoxic drugs (vinblastine, bleomycin, interferon alfa and molgramostim (recombinant granulocyte–macrophage colony stimulating factor)) may be used. The tumour is very radiosensitive. Systemic low-dose interferon alfa has been given but the use of highly active antiretroviral therapy (HAART) has greatly improved the management of AIDS-related Kaposi's sarcoma.

Vincristine, doxorubicin and bleomycin chemotherapy has been standard for aggressive disease but new regimens employing etoposide, angiogenesis inhibitors (e.g. bevacizumab) and sorafenib are being investigated. Ciclosporin-induced Kaposi's may be reversed by sirolimus (rapamycin). This is a macrolide antibiotic with immunosuppressive antiproliferative and antiangiogenic properties. It inhibits mTor (the mammalian target of rapamycin) and is anti-VEGF and restores programmed cell death. It reduces lymphocyte proliferation by inhibiting responses to IL2. HHV-8 upregulates VEGF and therefore induces angiogenesis.

Moles and melanoma 11

Melanocytic naevi

Melanocytic naevi are commonly referred to as 'naevi' or 'moles'. They are common and occur in all Caucasians. They are benign proliferations of melanocytes that arise from the neural crest early in fetal life. Some are present at birth or shortly thereafter (*congenital naevi*) and are larger than acquired naevi. They are permanent. Most, however, develop gradually during childhood, more rapidly in adolescence, peak in the third decade and then tend to disappear after the forties; consequently, it is rare to find acquired pigmented naevi in the elderly. Density of naevi is proportional to skin colour (the paler the skin, the greater the density). Moles may be predetermined or induced by ultraviolet irradiation. Children born in Queensland, Australia, an area of intense solar ultraviolet irradiation, have higher total body melanocytic naevi counts than those born in other Australian states that are further from the equator, even though the prevalence is similar at birth. The highest densities are on the face, neck and outer arms. Since the number of melanocytic naevi is proportional to sun exposure, it is a risk marker for malignant melanoma. Exogenous growth hormone (including melatonin) is known to increase the growth rate of naevi, and naevus counts are increased following chemotherapy for haematological malignancies including lymphoma. This may be secondary to immunosuppression, since they are increased in children who have undergone renal transplantation. Neonatal phototherapy for hyperbilirubinaemia is a strong promoter of naevi development.

In childhood, most melanocytic naevi proliferate at the junction of the epidermis and the dermis, forming nests or thèques of cells with abundant cytoplasm containing melanin, and are known as *junctional naevi*. Subsequently, these melanocytes migrate into the dermal papillae and more deeply around appendages and neurovascular bundles. The superficial cells are still recognizable as naevus cells and continue to form melanin; they are taken up by melanophages in the stroma and are known as type A cells. Deeper cells are smaller and contain no melanin although tyrosinase and premelanosomes are present. These cells are arranged as a band or as an arborizing column in the deeper dermis, where they become spindle shaped and are known as type B cells. When there are nests of melanocytes both in the dermis and at the junction with the epidermis, they are known as *compound naevi*. If the junctional melanocytes stop proliferating then the epidermis returns to normal and the nests of cells are then found exclusively in the dermis and known as *intradermal* or *cellular naevi*.

Congenital melanocytic naevi have some features in common with compound naevi but the nests extend more deeply into the reticular dermis and subcutaneous fat. The melanocytes in a *blue naevus* are situated deep in the reticular dermis. Incidental light on the heavily pigmented cells at this level is reflected back to the naked eye as a blue rather than brown colour (a property of light, known as Tindel's effect). This naevus is regarded as a failure of melanocytes to arrive at the dermo-epidermal junction from the neural crest.

The *halo naevus* is a benign pigmented naevus surrounded by a patch of vitiligo, which is usually followed by elimination of the naevus and eventual repigmentation of the skin. The condition probably represents an autoimmune phenomenon since, histologically, there is a dense inflammatory cell infiltration of the naevus; serologically, antibodies against the cytoplasm of malignant melanoma cells may be identified in individuals with halo naevi.

Understandably, misconceptions surround moles, because of their associations with malignant melanoma. In particular, moles of the palms, soles and genitalia are not potentially dangerous and do not need to be removed: 10% of young men have moles on the palms, soles or genitalia and yet malignant melanoma is uncommon in these sites. Electrolysis of hair from compound naevi is not dangerous and excision of a benign mole does not provoke malignant change.

Most malignant melanomas arise from previously normal skin and there is no historical or histological evidence of a pre-existing benign mole. The rest arise either from congenital naevi or from dysplastic naevi and only sometimes from ordinary acquired moles.

CONGENITAL MELANOCYTIC NAEVUS

A large pigmented naevus that is present at or around birth in approximately 1% of all newborns and persists throughout life.

Clinical Features

Symptoms

An asymptomatic, sometimes disfiguring, pigmented blemish.

Morphology

It varies greatly in size, reaching many centimetres in some cases and very occasionally covering most of the integument (*giant hairy pigmented naevus*). However, most are small, although always greater than 1 cm in size (and thus larger than acquired naevi) (Fig. 11.1).

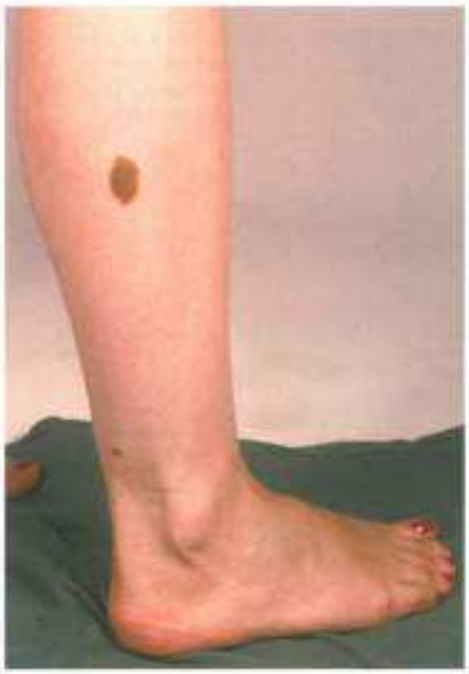


Fig. 11.1 Congenital melanocytic naevus. One percent of Caucasians have a congenital mole at birth. They are larger than acquired moles but vary in size. The risk of malignancy is slight but, as the leg is a common site for malignant melanoma, prophylactic excision is reasonable.

The lesion is usually raised, sometimes with small, raised pebbly (mamillary) projections. It may be smooth, warty, lobular or cerebriform and is round or oval in shape with accentuated surface skin markings. It varies in shade from a light tan to medium or dark brown, often with two colours, the darker shade being distributed centrally. The arrangement of the colours is generally uniform. There is an increase in pigmentation and hairiness at puberty.

Distribution

It may appear anywhere and usually has no systemic significance, although those that occur over the vertebral column may be associated with spina bifida or meningocoele.

Histopathology

They are either compound or intradermal melanocytic naevi and although they have many features in common with their acquired counterparts, there are distinctions. Congenital naevi tend to involve the deeper aspects of the reticular dermis and characteristically spread into the fibrous septae and adipose tissue of the subcutaneous fat (Fig. 11.2). The naevus cells involve sebaceous glands, hair follicles, arrector pili muscles and eccrine glands and also permeate nerves, lymphatics and blood vessels. Single cell and Indian-file arrangements of melanocytes are characteristic.

Management

Congenital melanocytic naevus do have a risk for potential malignant change, but it is very low given that malignant melanoma is uncommon and yet 1% of the population have congenital naevi. There is however a significant risk of malignant melanoma developing in a congenital giant hairy pigmented naevus (*bathing trunk naevus*).

The best advice is that these naevi should be excised, particularly in sites which cannot be easily observed, if this is technically possible without mutilation and cosmetic ill-effect, which, in practice, encompasses only the smaller ones, although tissue expanders have made surgery easier for larger lesions.

Q-switched ruby lasers have been used to remove the superficial naevus cells without scarring and this lightens the lesion, but the long-term effects are not known. It may be useful for disfiguring lesions where excision is not feasible.

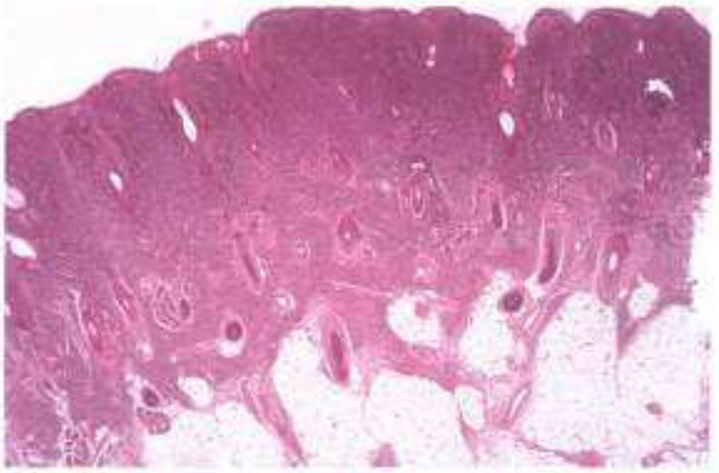


Fig. 11.2 Congenital melanocytic naevus. In this scanning view, massive melanocytic proliferation extends from the epidermis into the subcutaneous fat. All of the appendage structures appear to be surrounded by a mantle of naevus cells. The surface of the lesion has a warty appearance.

GIANT BATHING TRUNK NAEVUS

A rare extensive involvement of the skin with large diffuse pigmented naevi; it is present at birth and has a significant risk of malignant melanoma of the skin or nervous system.

Clinical Features

Symptoms

A disfiguring collection of large and giant moles on the skin.

Morphology

The naevi are various shades of brown; some are hairy and many are raised becoming more so with time. Some have papillomatous projections and the skin may become quite redundant in areas. Some are large and others are quite diffuse in their extent.

Distribution

The naevi are extensive (Fig. 11.3) and occur anywhere on the body but the condition is so named because the bathing trunk area is usually involved (Fig. 11.4).

Fig. 11.3 Giant hairy bathing trunk naevus. The naevi are extensive and present at birth.

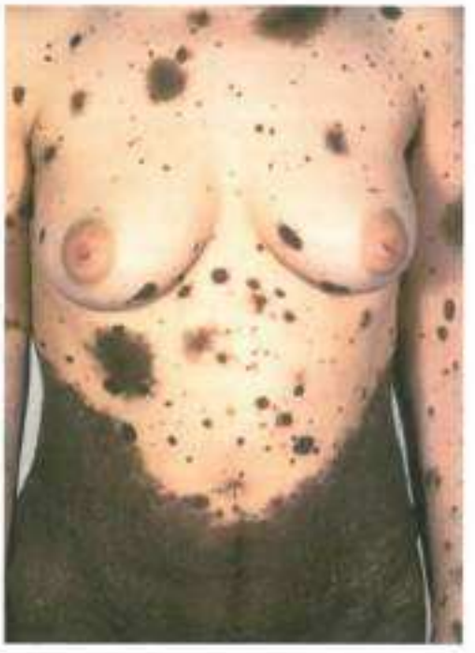


Fig. 11.4 Giant hairy bathing trunk naevus. The bathing trunk area is extensively involved. Large naevi are scattered elsewhere. She developed a cerebral melanoma.

Histopathology

The histological features of the congenital giant naevus are variable but may be similar to those of the more usual congenital lesion with, in addition, marked neurotization (Fig. 11.5). Neurofibromatous foci, blue naevi and even juvenile melanoma-like areas may be present.

Management

Malignant melanoma does complicate this condition, including childhood cases. The exact incidence is unknown because of the tendency to report only those examples that do eventuate in malignant melanoma and subsequently metastasize. Previously, prophylactic surgery was common practice, but excision of all the lesions is not usually technically feasible, and there is no evidence that it reduces an adverse clinical outcome. Malignant melanoma may also arise de novo and in the central nervous system. At present, observation of the skin and periodic brain scans and magnetic resonance imaging to detect neurocutaneous melanosis are probably all that can be advised. Solar protection is mandatory.

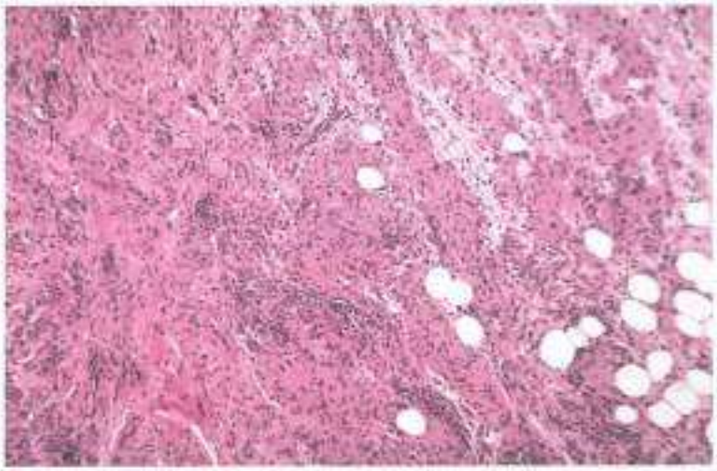


Fig. 11.5 Bathing trunk naevus. Neurotization (neural features), as shown in this field, is a very common phenomenon.

JUNCTIONAL MELANOCYTIC NAEVUS

An acquired melanocytic naevus occurring in the first few decades of life which may be predetermined or result from excess solar irradiation.

Clinical Features

Symptoms

Moles are quite asymptomatic and rarely itch.

Morphology

Usually no bigger than 0.5 cm in diameter, they are either flat or slightly raised and have a single dark brown colour (Fig. 11.6) or are two-toned.

Distribution

Anywhere on the skin.

Histopathology

The junctional naevus is the earliest stage in the evolution of the melanocytic naevus. Melanocytes proliferate to form discrete collections (nests) of naevocytes in the lower aspect of the epidermis and are usually situated within the epidermal ridges (Fig. 11.7). The individual cells are uniform, have pale or clear cytoplasm and often show rather evenly dispersed fine granules of melanin pigment. In heavily pigmented variants, melanin may be found within the cytoplasm of histiocytes (melanophages) in the papillary dermis.

Management

Any naevus with junctional activity has the potential for malignant change, but this is rare in comparison with their prevalence, for it is estimated that the average Caucasian has at least 25 moles. Some believe that individuals with a large number of junctional naevi have an increased risk of developing malignant change, but this may correlate with skin type 1. Junctional naevi may be excised for cosmetic reasons or for diagnostic purposes; otherwise they should be left alone to save the patient from unnecessary and unsightly scars.

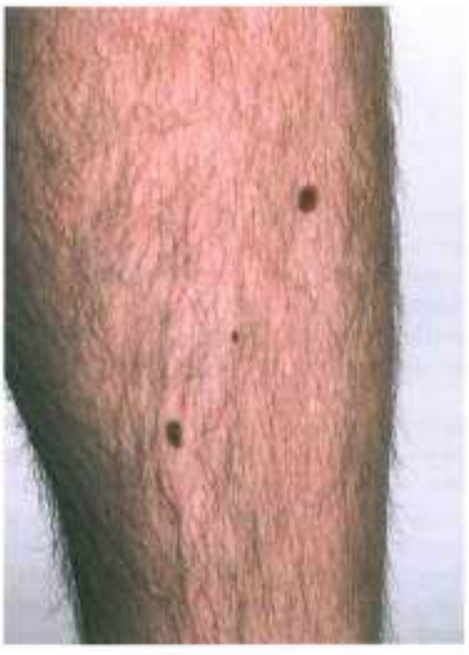


Fig. 11.6 Junctional naevi. The lesions are small, even, dark flat moles most commonly situated on the limbs and are quite benign.

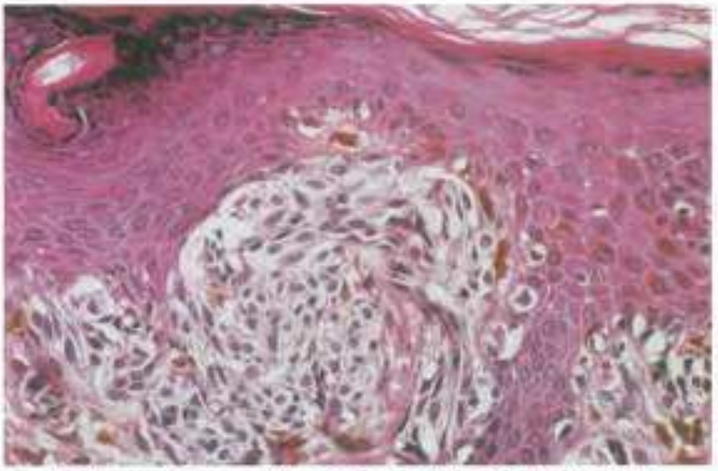


Fig. 11.7 Junctional naevus. A typical nest of uniform melanocytes is seen in the centre of the field. Note the pale cytoplasm and regular oval nuclei with prominent nucleoli.

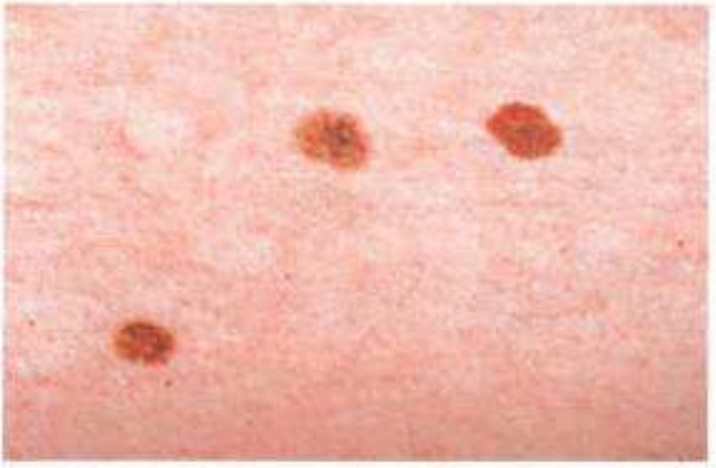


Fig. 11.8 Compound melanocytic naevus. These harmless moles are slightly raised, round and have evenly distributed brown pigment.

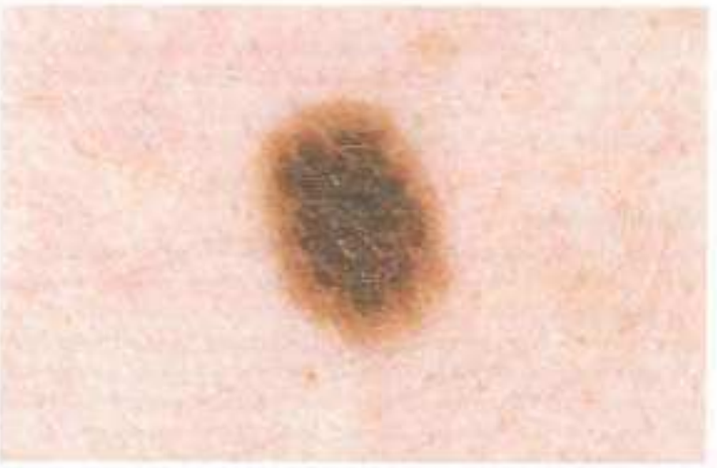


Fig. 11.9 Compound naevus. The lesion is slightly raised and oval. The pigment may be two-toned, for example darker centrally than at the margin.

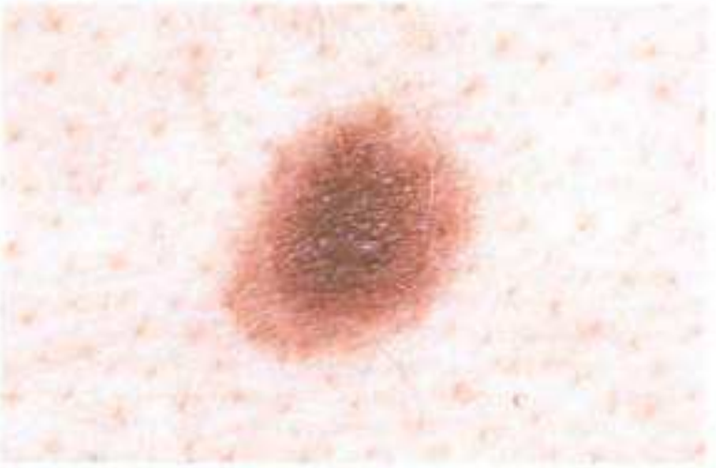


Fig. 11.10 Compound naevus. The lesion is raised and has two colours, a light brown at the margin and brown centrally, relatively evenly distributed.

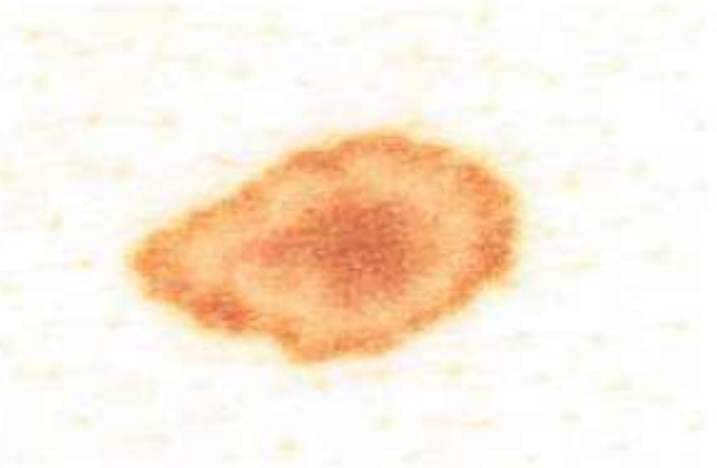


Fig. 11.11 Compound naevus (naevus en cocarde). There are two shades of pigment, brown at the margins then light brown and brown at the centre forming a rosette (French: *cocarde*).

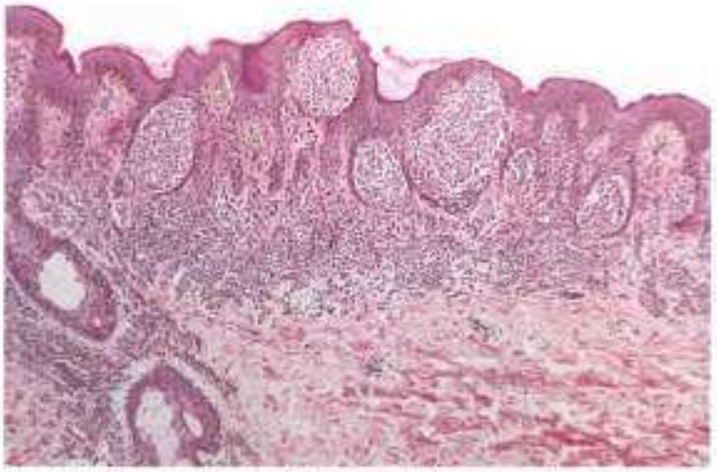


Fig. 11.12 Compound naevus. The surface of this specimen has a warty appearance. In addition to a junctional component, numerous melanocytes are present in the dermis.

COMPOUND NAEVUS

A raised pigmented acquired naevus of melanocytes.

Clinical Features

Symptoms

Usually asymptomatic.

Morphology

Compound naevi are pigmented, brown (Fig. 11.8), smooth surfaced, sharply defined and round or oval (Fig. 11.9). They may be slightly raised or considerably more so, since the naevus cells may expand the dermal papillae and throw the epidermis into a series of folds. They feel soft and may be two-toned in colour (Fig. 11.10), sometimes forming a rosette (Fig. 11.11). The pigment is not always completely even. Coarse hairs may project from their surface.

The important distinction from malignant melanoma is that the arrangement of pigment within the lesion is uniform. The shape is generally, but not entirely, even and is either oval or round. Although close inspection is very important, it is often helpful to examine such a mole from a distance initially, since this gives a better idea of whether the arrangement of colour and shape is uniform and regular, in contrast to the disordered appearance of a malignant melanoma. The surface is usually smooth and the skin creases are generally preserved.

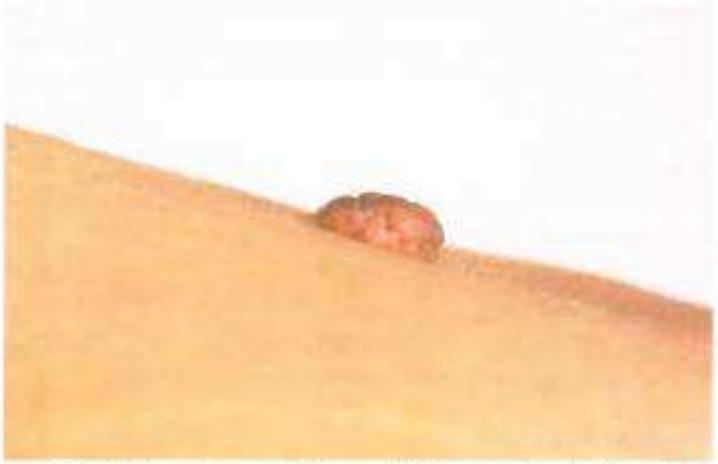


Fig. 11.13 Intradermal naevus. This mamillated naevus is raised and loses its pigment as it becomes intradermal. It has no malignant potential.

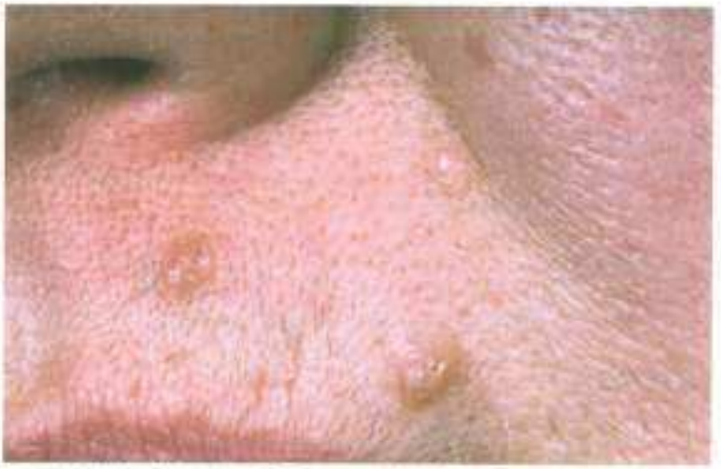


Fig. 11.14 Intradermal naevi. These are soft/sh, flesh coloured papules. They are common on the face and may be shaved off, under local anaesthesia.

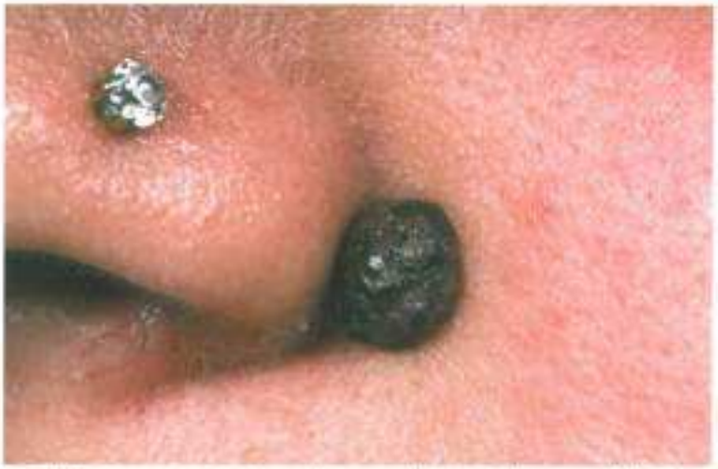


Fig. 11.15 Compound melanocytic naevus. The nests of naevus cells in this fleshy type of mole may either be predominantly intradermal (Fig. 11.14) or in this pigmented variety may also be at the dermo-epidermal junction.

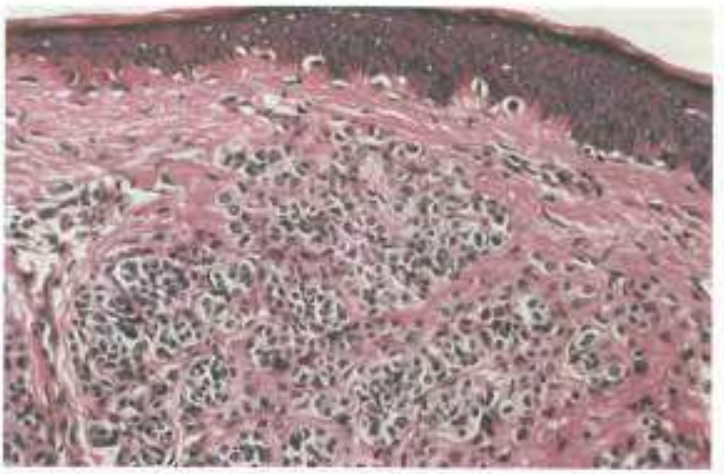


Fig. 11.16 Intradermal naevus. The epidermis is flattened over the lesion. Scattered melanocytes are present but there is no junctional activity. In the dermis are non-pigmented melanocytes, many of which have rather hyperchromatic nuclei.

Histopathology

The compound melanocytic naevus shows collections (thèques) of naevocytes within the dermis in addition to the junctional zone (Fig. 11.12). Areas may show nests appearing to 'drop off' into the papillary dermis. Melanin production may be retained superficially, but typically the deeper aspect of the naevus shows little or no pigmentation. The dermal component often appears compact and consists of uniform, smaller cells with darker staining nuclei. Mitotic activity is not present. Compound naevi may be associated with marked squamous epithelial proliferation, which may result in a warty or verrucous clinical appearance.

Management

There is no need for treatment except for cosmetic reasons. Compound naevi may be surgically excised or particularly raised ones may be shaven off flush to the skin and the base gently cauterized.

INTRADERMAL (NAEVOCELLULAR) NAEVUS

An acquired flesh-coloured intradermal melanocytic naevus.

Clinical Features

Symptoms

Usually asymptomatic but sometimes cosmetically unacceptable.

Morphology

It is small, soft, dome shaped (Fig. 11.13), sometimes with surface telangiectasia, occasionally hairy and flesh-coloured (Fig. 11.14) as opposed to a compound naevus which is pigmented (Fig. 11.15). Facial lesions sometimes temporarily become inflamed, possibly because of underlying acne.

Distribution

Anywhere on the skin, particularly on the face and scalp.

Histopathology

As the naevus matures, the junctional component is lost, leaving an entirely intradermal lesion (Fig. 11.16). With the increasing depth, the naevocytes become smaller with darkly staining nuclei and little cytoplasm. They may become a spindle-shaped and frequently show 'neural' features.

Management

Small ones can be shaved off flush to the skin and the base gently cauterized.

BLUE NAEVUS

This blue-coloured mole consists of melanocytes in the lower dermis as they migrate from the neural crest to the dermo-epidermal junction.

Clinical Features

Symptoms

An asymptomatic blue mole.

Morphology

A round blue papule or nodule with a smooth surface (Fig. 11.17). It is usually less than 0.5 cm in diameter but may be larger (Fig. 11.18).

Distribution

Anywhere but particularly the dorsa of the hands or feet, the face and in the mouth (Fig. 11.19).

Histopathology

The histological hallmark of the simple blue naevus is the heavily pigmented dendritic melanocytes (Fig. 11.20), which may be found singly or arranged in interlacing fascicles. The melanocytes are typically elongated, irregular and often branched; their pigment content is such that all cellular details are obscured. Associated with the melanocytes are melanin-containing macrophages and a variable degree of scarring. The refraction of light on the melanocytes at this level gives rise to the blue appearance. A cellular type occurs that has, in addition, islands of larger cells arranged in a neuroid manner.

Management

It is entirely benign. Multiple lesions occasionally occur. Malignant blue naevi occur but are extremely rare.

NAEVUS OF OTA

A unilateral bluish discoloration of the skin around the eye and involving the eye caused by dermal melanocytes; it is common in Asians.

Clinical Features

Symptoms

A disfiguring blue blemish occurring after birth which gradually darkens.

Morphology

This naevus forms as an extensive, bluish, patchy, speckled pigmentation (Fig. 11.21), which may be brownish in superficial areas. The conjunctivae may be stained brown but the sclera blue.

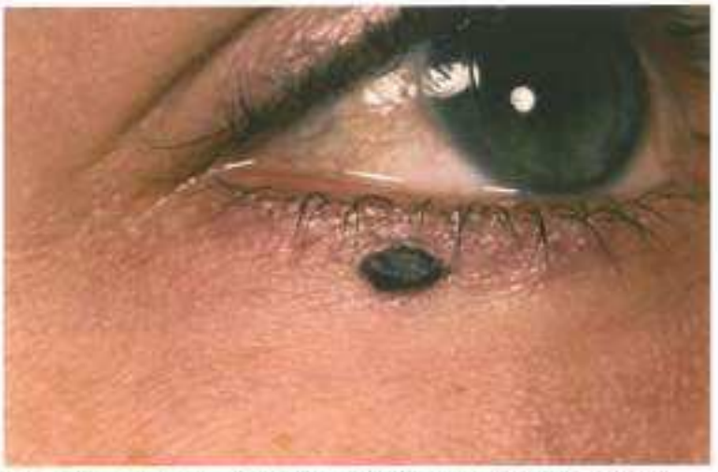


Fig. 11.17 Blue naevus. The lesion is raised and blue. The naevus cells are present in the lower dermis and incidental light refracts their pigment as a blue colour.

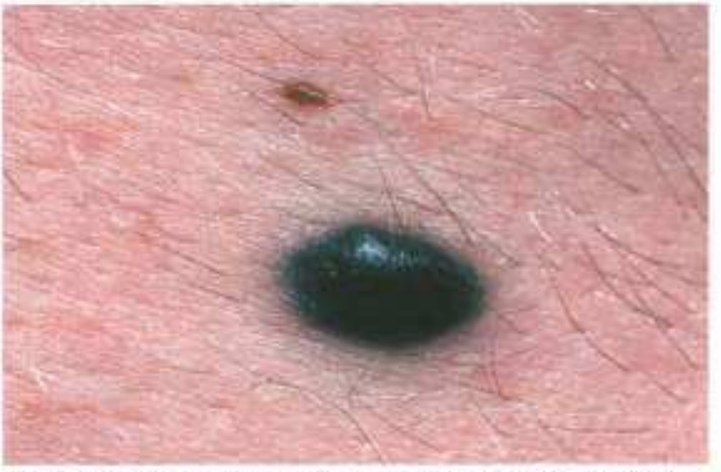


Fig. 11.18 Cellular blue naevus. The naevus is occasionally more cellular and larger than usual. The blue-grey colour is still remarkable.

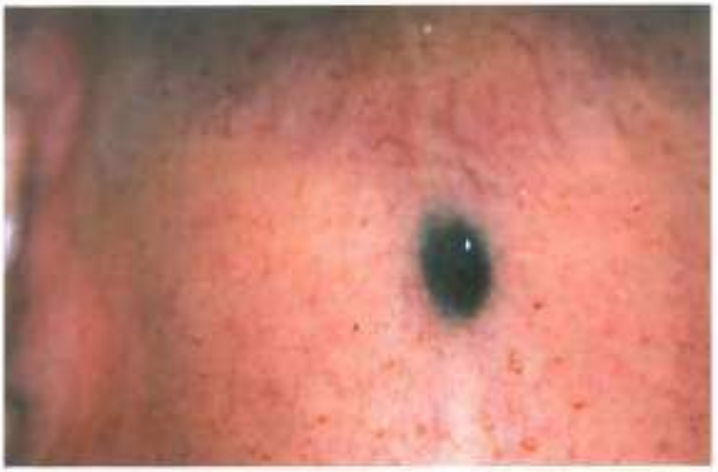


Fig. 11.19 Oral blue nevus. The classic sites for a blue naevus are the face, mouth and backs of the hands and feet.

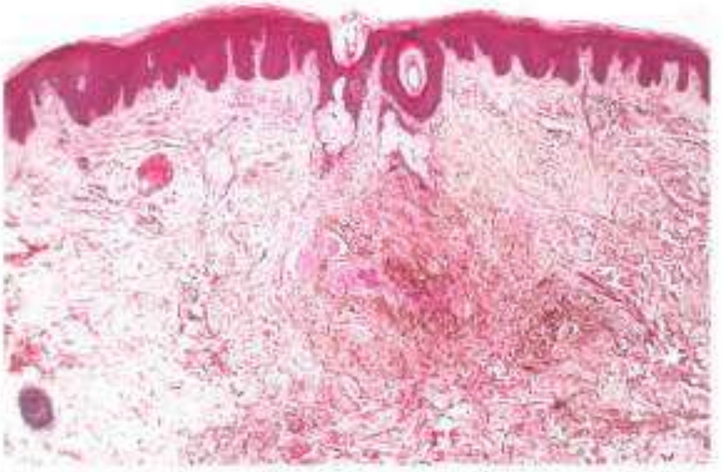


Fig. 11.20 Blue naevus. No junctional or upper dermal component is present. Situated within the reticular dermis is an irregular, heavily pigmented spindle cell lesion.

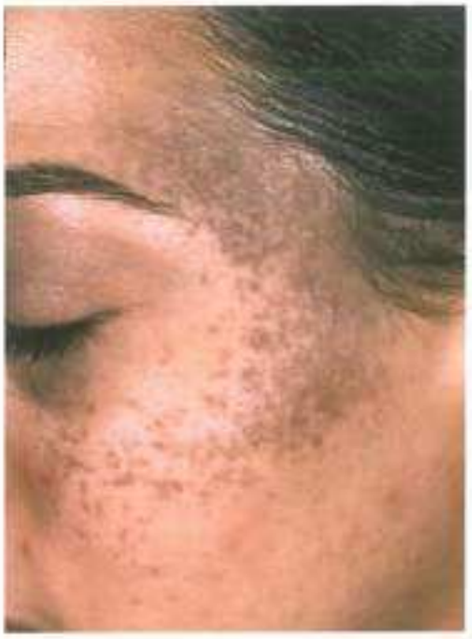


Fig. 11.21 Naevus of Ota. This blue blemish occurs most commonly in Oriental patients. The face is affected unilaterally and the lesion is permanent.

Distribution
Naevus of Ota occurs in the areas supplied by the ophthalmic and maxillary divisions of the trigeminal nerve. It is unilateral and often has a reticular or geographical pattern. The sclera is often involved (Fig. 11.22). If it occurs in the areas supplied by the posterior supraclavicular and lateral brachial cutaneous nerves, it is known as the *naevus of Ito*.

Histopathology
In the naevus of Ota, dendritic pigmented melanocytes are present in the deeper layers of the reticular dermis.

Management
Malignant change is very rare but has been reported. Q-switched ruby laser therapy causes selective photothermolysis and lightens the stain, which is otherwise permanent.

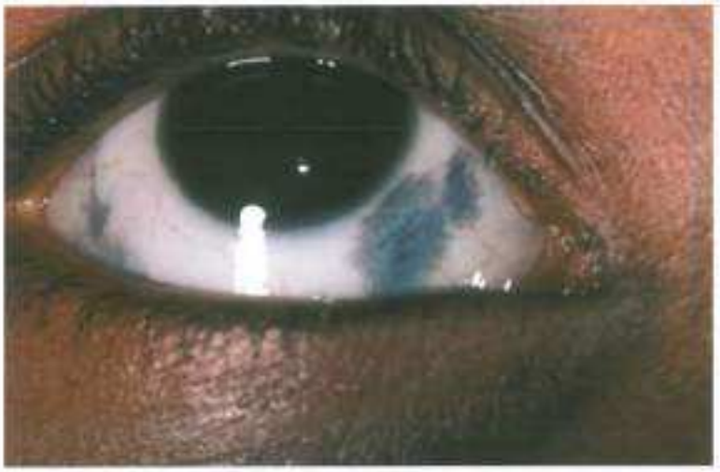


Fig. 11.22 Naevus of Ota. The sclera is often involved in addition to the face. It is quite benign. The colour may be brown or blue.

NAEVUS DEPIGMENTOSUS (ACHROMICUS)
A congenital circumscribed area of depigmentation.

Clinical Features
Symptoms
A white patch on the skin.

Morphology
A well-defined, large, irregular, round, non-progressive white patch (Fig. 11.23).

Distribution
Anywhere (Fig. 11.24) but particularly on the buttocks and trunk.

Histopathology
The synthesis of normal melanosomes and their transport to keratinocytes is functionally abnormal in naevus depigmentosus. Ultrastructurally the number of melanosomes is substantially reduced. They are of variable morphology and aggregated in melanocytes that otherwise appear quite normal in number and shape. The diagnosis is not difficult but Wood's lamp examination will distinguish between the off-white accentuation of naevus depigmentosus and the chalky white of vitiligo.

Management
It is essentially an isolated phenomenon and quite harmless, although occasionally mental retardation and epilepsy have been recorded.

Fig. 11.23 Naevus depigmentosus. It is a unilateral round area of pigment that may be white or off-white. It is present at birth or shortly thereafter. It can be distinguished from vitiligo because it does not have a hyperpigmented border.

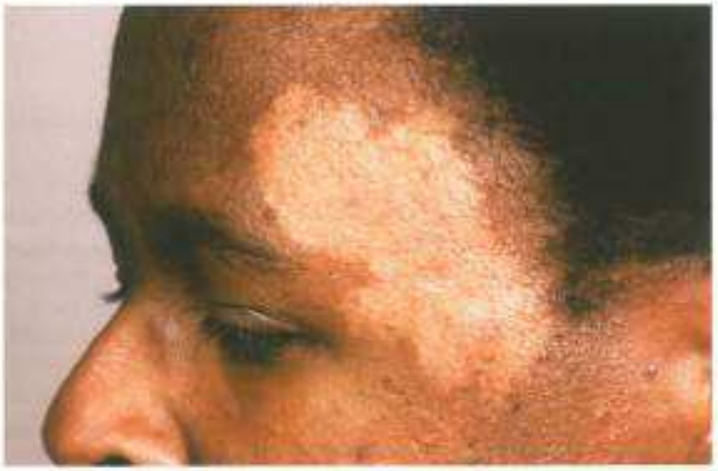


Fig. 11.24 Naevus depigmentosus. There is loss of pigment as a result of a reduction in the number of the functionally abnormal melanocytes.

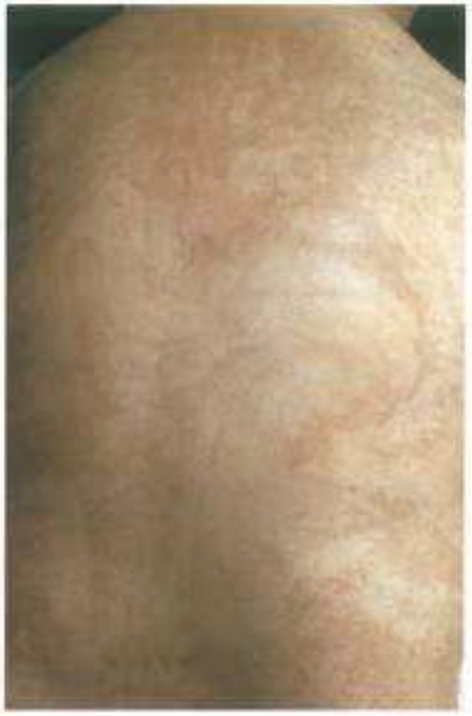


Fig. 11.25 Incontinentia pigmenti achromicus. A distinctive whorled hypopigmentation occurs on the trunk and is usually present at birth.

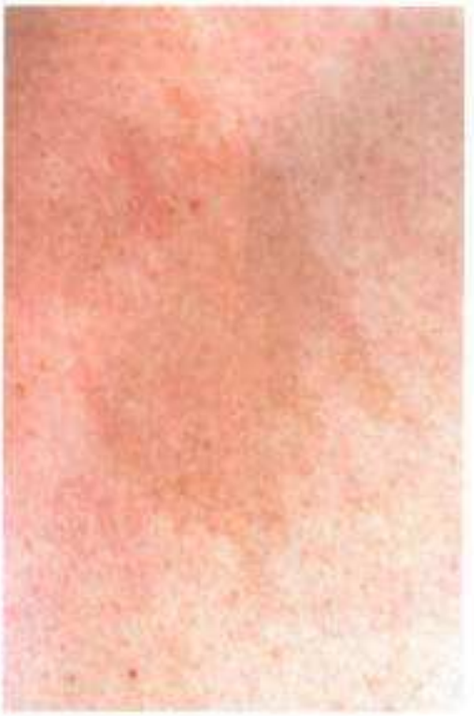


Fig. 11.26 Café-au-lait patch. These may occur singly at birth as a harmless naevus or gradually develop after birth as part of neurofibromatosis or other genetic disorders.

INCONTINENTIA PIGMENTI ACHROMICUS OF ITO

Also known as *hypomelanosis of Ito*, it is a sporadic hypopigmented anomaly producing linear and swirled patterns along the lines of Blaschko, sometimes associated with abnormalities of the central nervous, ocular and musculoskeletal systems.

Clinical Features

Symptoms

White streaks are usually present at birth.

Morphology

There is a loss of pigmentation in hypomelanosis of Ito that occurs in a very distinctive whorled pattern.

Distribution

The loss of pigmentation may be unilateral or bilateral and the trunk is usually involved (Fig. 11.25).

Histopathology

The histopathology is similar to that of naevus depigmentosus (see above).

Management

Although usually sporadic, familial cases have been reported and the condition is thought to be caused by somatic mosaicism. Talon cusps protrude on the palate surface of the incisor crown and are a specific marker for the condition. It can be distinguished from incontinentia pigmenti because there is no preceding inflammatory stage and from linear and whorled naevoid hypomelanosis because there are streaks of macular hyperpigmentation along the lines of Blaschko (cardiac and neurological defects have been associated with this condition). Some regard naevus depigmentosus, hypomelanosis of Ito and linear and whorled naevoid hypermelanosis as a heterogeneous collection of disorders indicative of underlying genetic mosaicism and do not separate them out.

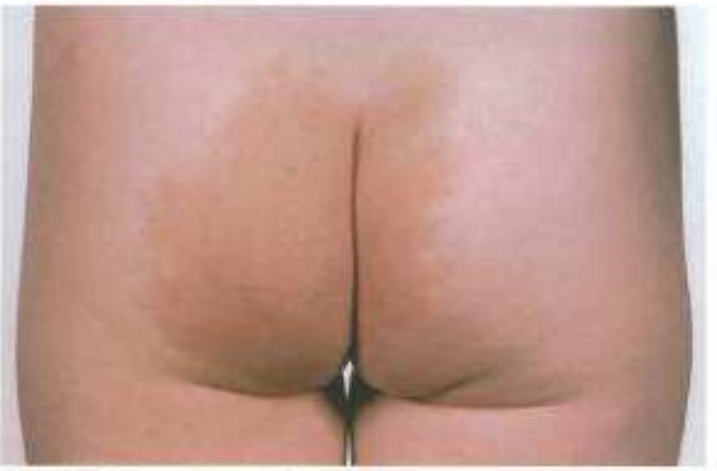


Fig. 11.27 Café-au-lait patch. Single patches are common in otherwise healthy individuals. The patch is quite flat and a light coffee colour.

CAFÉ-AU-LAIT PATCH

A well-circumscribed patch of hyperpigmentation present at birth as a harmless naevus or occurring with certain genetic disorders.

Clinical Features

Symptoms

A pigmented blemish on the skin.

Morphology

A well-circumscribed, small (Fig. 11.26) or large (Fig. 11.27), round or oval, pale brown patch. If the outline is smooth, it has been likened to the coast of California and if jagged or shaggy to the coast of Maine. Café-au-lait patches are common and particularly so in black skin. Multiple lesions suggest a systemic disturbance.

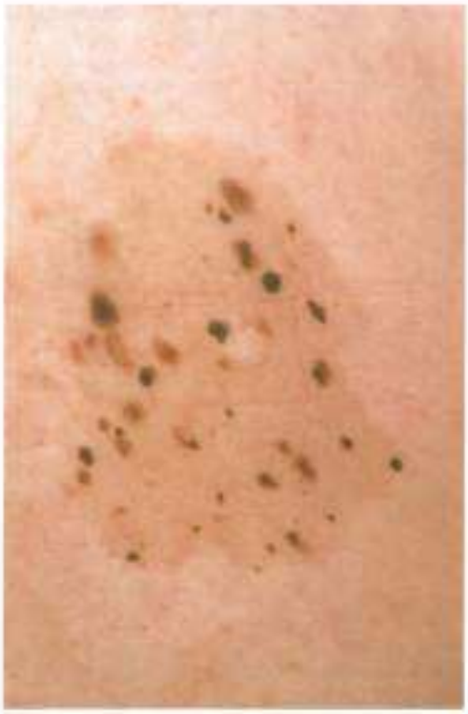


Fig. 11.28 Naevus spilus. There are dark brown flat macules occuring within a background of a more lightly pigmented patch. This macular type remains stable.

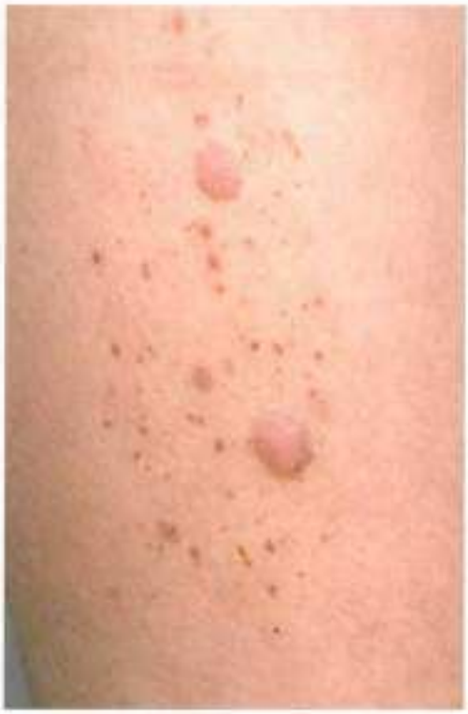


Fig. 11.29 Naevus spilus papulosus. There is a well-defined oval flat area of hyperpigmentation that contains dark macules and flesh-coloured papules. It has a dynamic course. The darker macules and papules develop during adolescence.

Distribution
Anywhere on the skin.

Histopathology
There is increased melanin content of the melanocytes and keratinocytes.

Management
A single café-au-lait patch is of no significance, but multiple lesions, particularly more than six, are likely to be associated with neurofibromatosis, Albright's syndrome or a ring chromosome defect (Ch. 20).

NAEVUS SPILUS
A speckled and lentiginous naevus that develops in childhood.

Clinical Features
Symptoms
Naevus spilus is a blemish on the skin.

Morphology
There are dark brown, flat macules occurring within a background of a large, more lightly pigmented patch (Fig. 11.28). It is a 'spotty' abnormality (Greek *spilos*: spot). Raised flesh-coloured papules may also occur within the naevus (Fig. 11.29).

Distribution
The naevus spilus may be discrete or segmental and may occur anywhere on the body.

Histopathology
The background macule in naevus spilus consists of increased numbers of melanocytes. The flat, dark macules are lentiginous melanocytic hyperplasia and the dark areas are naevomelanocytes in the epidermis and/or dermis. The lesion is characterized by epidermal lentiginous hyperplasia in association with a junctional or compound naevus. Spitz naevi may also occur.

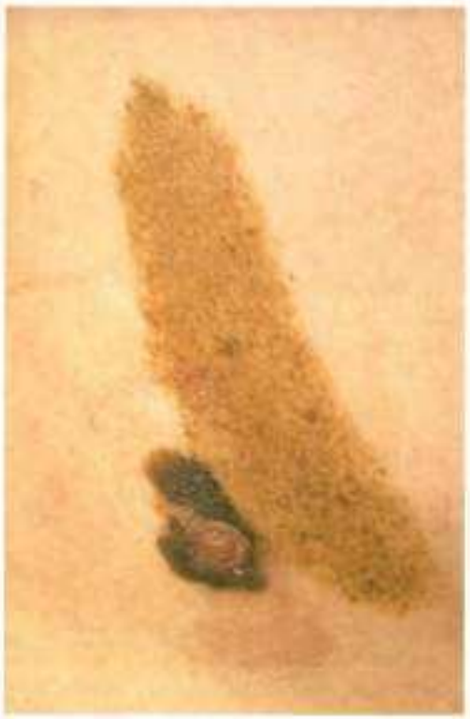


Fig. 11.30 Malignant melanoma developing in naevus spilus. A black plaque with a central reddish nodule has developed to one side of a large congenital pigmented patch with dark macules within it (naevus spilus) in this 60-year-old female.

Management
The naevus spilus usually occurs alone but is part of the phakomatosis pigmentovascularis syndrome (Ch. 8) and is occasionally associated with neurofibromatosis. It may, extremely rarely, transform to malignant melanoma (Fig. 11.30).

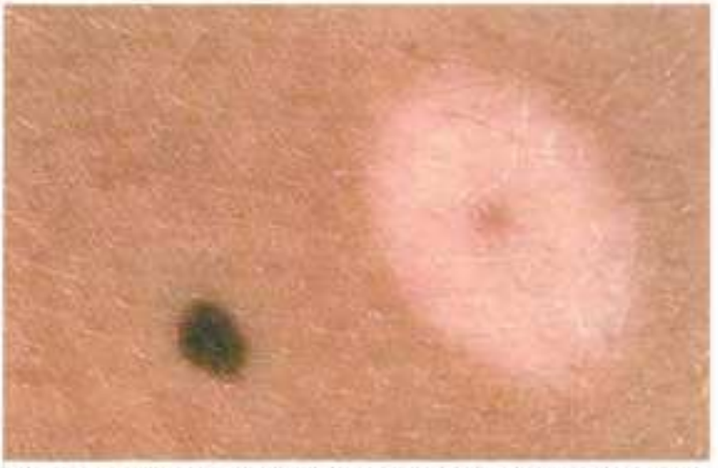


Fig. 11.31 Halo naevus. An area of vitiligo surrounds the mole, which has almost disappeared. The skin will eventually repigment. There is a compound naevus on the left.

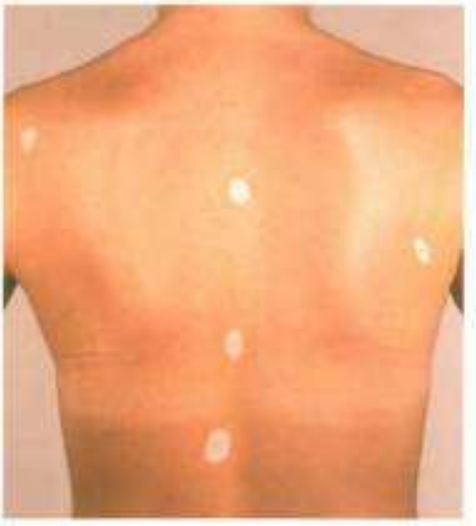


Fig. 11.32 Halo naevus. Multiple lesions may occur. There is an increased association with vitiligo.

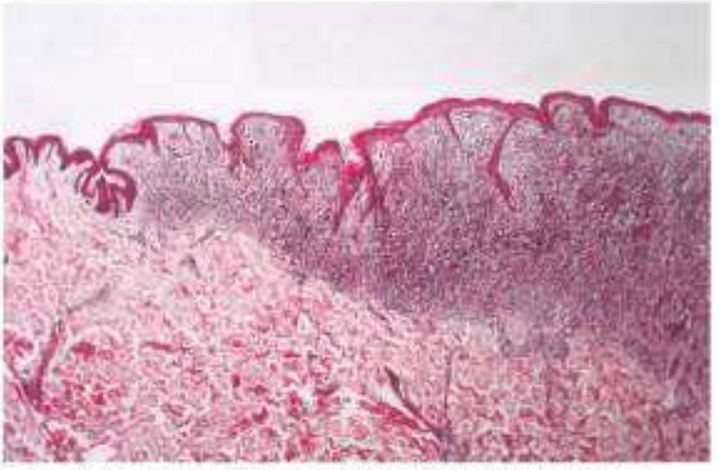


Fig. 11.33 Halo naevus. The lesion, which is sharply demarcated from the normal skin (left), shows a lichenoid inflammatory infiltrate.

HALO NAEVUS (SUTTON'S NAEVUS)

A white ring appears around a benign melanocytic, which subsequently disappears. The resultant white area eventually repigments.

Aetiology

The condition occurs in youth and is an autoimmune phenomenon. Circulating antibodies directed towards melanoma cytoplasmic antigens in vitro have been found. There is an increased incidence of vitiligo.

Clinical Features

Symptoms

The appearance of a white area around a mole may give rise to alarm.

Morphology

Uniform and complete depigmentation surrounds the naevus (Fig. 11.31), which subsequently disappears leaving the skin completely white. Repigmentation occurs some years later. Multiple lesions may be present (Fig. 11.32).

Distribution

The lesion may occur anywhere.

Histopathology

There is usually a compound melanocytic naevus, which is surrounded by an intense chronic inflammatory cell infiltrate of predominantly lymphocytes and histiocytes with occasional plasma and mast cells often in a lichenoid distribution (Fig. 11.33).

At an early stage, melanocytes may easily be seen, both as nests and as individual cells, but as the lesion progresses they become increasingly difficult to identify. With the destruction of pigment-containing naevus cells, the released melanin is taken up by macrophages, which, in older resolving lesions, may be all that is left to mark the scene of the previous activity. The histology of the surrounding halo is characterized by an absence of any visible melanin pigment and associated with a negative dopa reaction.

Management

The lesion is quite harmless and the patient can be reassured.

MAYERSON'S NAEVUS

A benign melanocytic naevus, surrounded by eczema.

Clinical Features

Symptoms

There is an itchy rash occurring around a mole.

Morphology

There is redness and scaling around one or several melanocytic naevi (Figs 11.34 and 11.35).

Distribution

It may occur anywhere on the body.

Histopathology

There is focal parakeratosis, irregular acanthosis and spongiosis, which overlie a junctional naevus. There is a superficial perivascular lymphohistiocytic infiltrate without disturbance of the melanocytes.

Management

Mayerson's naevus occurs in youth and is of unknown aetiology, although it may represent a cell-mediated response analogous to the Sutton's halo naevus. It is quite benign and reassurance is all that is required. The eczema resolves either spontaneously or with a topical steroid and the naevus remains unchanged.

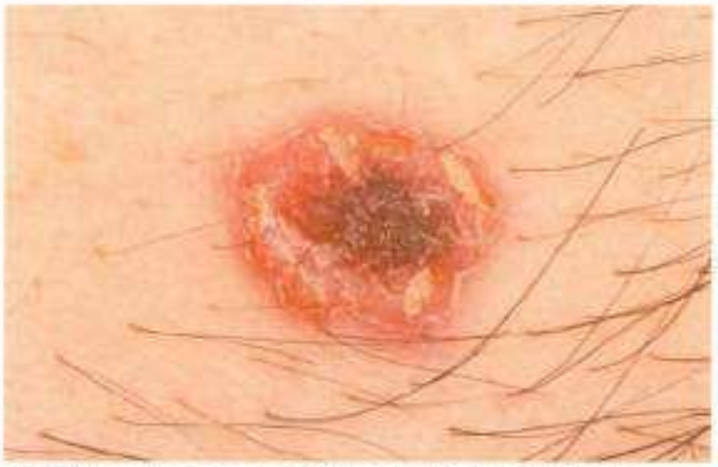


Fig. 11.34 Mayerson's naevus. A patch of eczema surrounds a benign melanocytic naevus, probably as a result of a cell-mediated reaction.

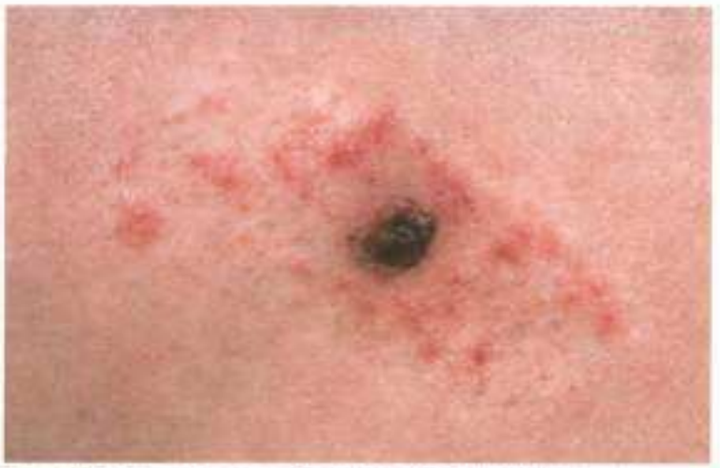


Fig. 11.35 Mayerson's naevus. Eczema around a pigmented naevus is an uncommon but benign phenomenon that resolves with topical steroids.

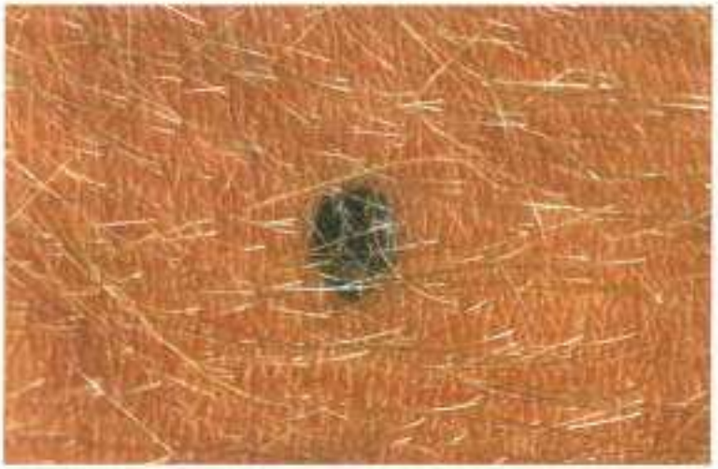


Fig. 11.36 Pigmented spindle cell tumour of Reed. The lesion is very heavily but evenly pigmented. It is benign, but it was excised to establish its nature.

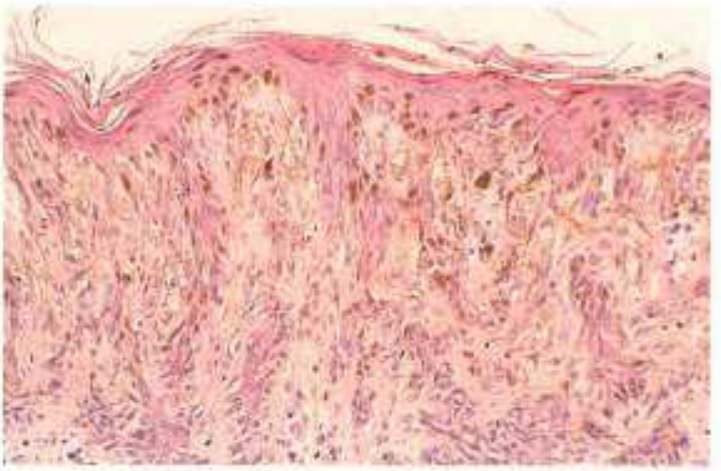


Fig. 11.37 Pigmented spindle cell tumour, junctional type. This example shows much pigment within the lesion and in the melanophages of the papillary dermis.

PIGMENTED SPINDLE CELL TUMOUR OF REED

A deeply pigmented, acquired melanocytic naevus that occurs in young adults.

Clinical Features

Symptoms

The dark or black colour may suggest a malignant melanoma.

Morphology

A very well-defined, heavily pigmented, black papule (Fig. 11.36) or nodule.

Distribution

It is more common on the proximal limbs.

Histopathology

This tumour may be junctional or compound involving the papillary dermis, but it is never solely dermal in location. It is composed predominantly of heavily pigmented spindle cells (Fig. 11.37), although epithelioid cells are sometimes in evidence. The lesion is symmetrical and sharply demarcated at its lateral borders. Compound lesions show maturation (a decrease in cell size and quantity of cytoplasm) with depth. Although mitoses are usually absent, on rare occasions tumours may show (invariably normal) mitotic figures. There is no significant pleomorphism, and Pagetoid features are uniformly absent. A frequent finding is the presence of scattered eosinophilic hyaline globules (compare with juvenile melanoma, below), and there is often a lymphocytic host response.

Management

It should be excised to exclude a malignant melanoma.

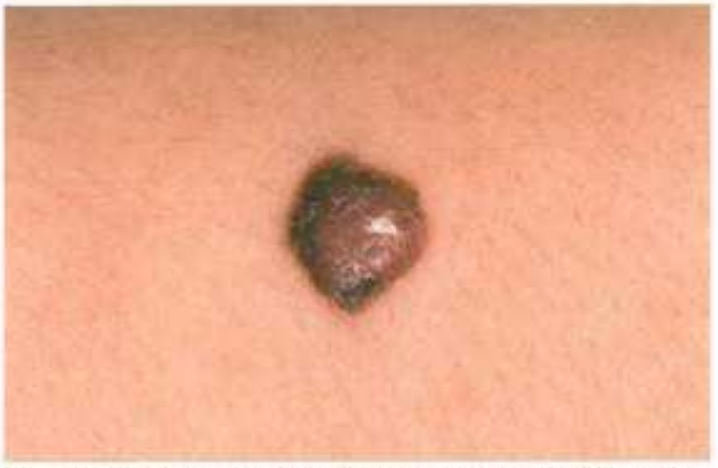


Fig. 11.38 Spitz naevus. The lesion is heavily pigmented; its occurrence in this 3-year-old should suggest a benign rather than malignant lesion.

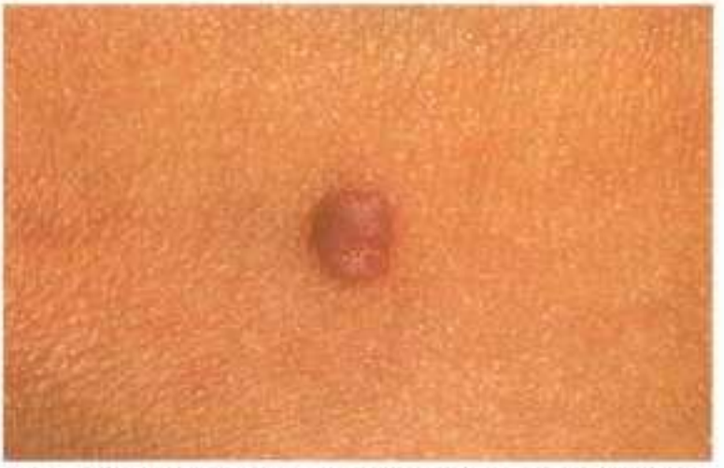


Fig. 11.39 Spitz naevus. This lesion in an 8-year-old child is red/brown in colour and dome shaped. This is the classical lesion described by Dr Sophie Spitz in 1948.

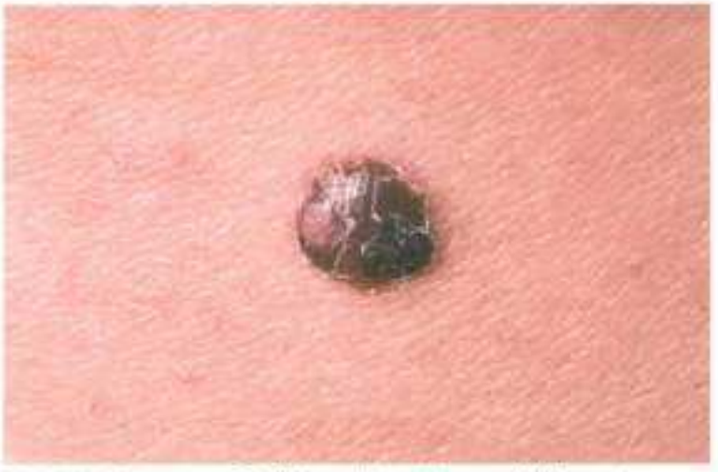


Fig. 11.40 Spitz naevus. This Chinese girl was 14 years old. Malignant melanoma is very rare at this age, but the lesion should be excised for pathology. This dark dome-shaped nodule was benign.

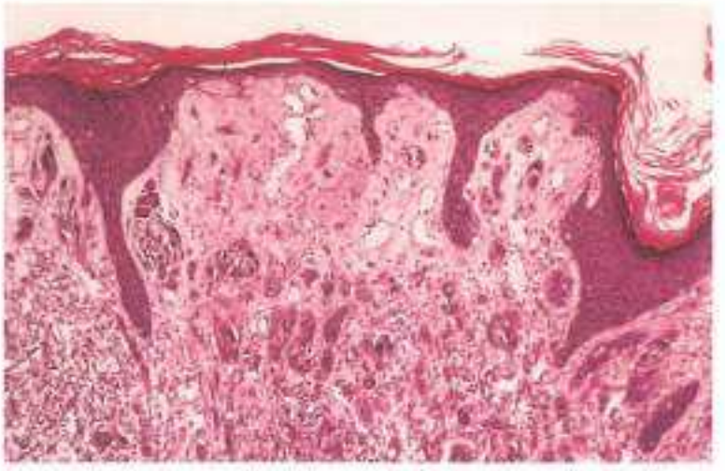


Fig. 11.41 Spitz naevus. There is hyperkeratosis, irregular acanthosis and in the superficial dermis ectatic vessels. The melanocytes are large, atypical and angulated with abundant eosinophilic cytoplasm.

SPITZ NAEVUS (JUVENILE MELANOMA)

A rare, benign naevus that may be mistaken for a malignant melanoma.

Clinical Features

Symptoms

A raised lesion appearing in childhood or later.

Morphology

Well-defined, dome-shaped (Fig. 11.38), red-brown (Fig. 11.39) or darker papule or nodule (Fig. 11.40) with a smooth surface.

Distribution

Usually occurs on the face, head, neck or lower extremity.

Histopathology

Spitzoid neoplasms are problematic because of their disturbing morphology and pathology. The classic Spitz naevus is red/brown in colour but variants are now described which include spindle cell tumour of Reed, Pagetoid Spitz, hyalinizing desmoplastic Spitz and an atypical Spitz tumour with superficial spreading melanoma-like potential (particularly seen in females on the thigh). In the main, it is an uncommon, benign variant of a compound naevus that is characterized by its pleomorphic appearance. It shows a striking symmetry, with melanocytic proliferation confined within the lateral borders of the lesion (Fig. 11.41). This is in contrast with malignant melanoma, in which typically junctional and/or dermal involvement is present around the main tumour mass. The cells of the superficial aspect of the juvenile melanoma may have an epithelioid or, more commonly, a spindle cell appearance and characteristically have abundant eosinophilic cytoplasm with rather large but typically uniform nuclei. Mononuclear and multinucleate giant cells may be present but these show little nuclear pleomorphism compared with those of a malignant melanoma. Juvenile melanoma usually has little pigment present; its pink coloration is caused by ectatic blood vessels, which are often found in its stroma. Mitotic activity may be seen but only in the superficial component of the tumour. The deeper aspect of the lesion shows evidence of maturation as would be expected in a benign compound naevus.

Management

Malignancy is rarely suspected before the lesion has been excised but may be reported as such because of the histological overlap with malignant melanoma; in childhood, the lesion is very unlikely to be malignant. However if there are atypical features pathologically, such as ulceration, large size, asymmetry, hypercellularity, lack of maturation and mitoses that are atypical or deep or more prominent, then a wider excision should be considered. Juvenile melanomas are not always easy to categorize and may represent part of a continuum rather similar to that between keratoacanthoma and squamous cell carcinoma and between lymphomatoid papulosis and cutaneous T-cell lymphoma.

Malignant melanoma

A potentially fatal skin cancer that arises from melanocytes, probably secondary to ultraviolet light irradiation which may metastasize via lymphatics and the circulation.

Aetiology

Although malignant melanoma is still an uncommon tumour, it is becoming less so and consultations regarding potential lesions are very common indeed. The incidence of malignant melanoma has doubled in a decade in Scandinavia and Australia and tripled in the USA in the last three decades. In Arizona, it has quadrupled in the Caucasian without rising at all in the Hispanic population. Similar increases are being seen in the UK where the incidence is approximately 5 new cases per 100 000, but this may be an underestimation. Approximately 1000 patients die of the disease every year, which is a similar number to those who die of carcinoma of the cervix. Queensland, Australia has the highest incidence in the world, 50 cases per 100 000 (whereas it was 16 per 100 000 in 1965). In the USA, it is the fifth most common cancer and lifetime analysis suggests that 1% will develop a malignant melanoma during their lifetime. However, there is evidence that melanoma mortality has reached a plateau in Australia.

Ultraviolet light is the most important cause, and the incidence of malignant melanoma in those with a susceptible skin type increases with proximity to the equator. The death rate from melanoma increases by 10% with a 2% decrease in latitude, suggesting that melanoma mortality is proportional to the amount of ultraviolet energy reaching the earth's surface since this is a function of latitude.

Mutations in certain rare high penetrance genes, particularly CDKN2A, have been found in some families with predisposition to malignant melanoma, but at present it is the phenotype that is most useful in predicting risk. Thus, the red-haired, blue-eyed, freckled individual, with poor tanning and high burning capability, has the greatest predisposition. In Los Angeles, this skin type has 12 times the incidence of melanoma compared with the local Chinese or Japanese population.

The type of exposure is thought to be important. Whereas solar keratoses, and basal and squamous cell carcinomas occur in those who are chronically exposed, the superficial spreading and nodular malignant melanoma are much more evident in indoor (white collar, well paid) than in outdoor (blue collar, poorly paid) workers. It is, therefore, suggested that intense but infrequent exposure once or twice a year, on vacation, may be more important than chronic continuous exposure. The exception is the lentigo maligna melanoma, which is a disorder of the elderly and seems to be related to chronic cumulative solar exposure. Sun exposure during childhood and adolescence may be important in that migrants from the UK to Australia have the same risk of developing malignant melanoma as Australian counterparts if they arrive before the age of 10 years but only one quarter of the risk if they arrive after the age of 15. Five or more significant blistering sunburns before 15 years of age have also been thought to increase the risk.

Malignant melanoma is rare in childhood and adolescence, is seen frequently in those aged 20–30 and is most common in those aged 30–50. The leg is the most common site in women and the back in men. The leg may be more vulnerable because many women do not wear stockings in the summer which in any case are poor physical protection from ultraviolet light. The truncal distribution in males may be explained by the tendency of men to strip to the waist when mowing the lawn or working outside. Malignant melanoma is very rare on the buttocks and in females on the scalp. It may be that the covered areas of the legs and trunk are more susceptible, being previously untanned, to intermittent intense exposure than the face and back of the hands. Some have proposed the theory that the melanocytes are less stable on covered areas (which are the areas most associated with naevi) than on the face and that mutagenesis may occur more easily.

The acral lentiginous melanoma is rare in Caucasians but is the most common melanoma to be found in Oriental and black-skinned patients. It occurs on palmar and plantar skin and under the nails. It does not appear to be associated with sunshine or naevi. Trauma may be a factor.

Nodular malignant melanoma is twice as common in males and usually presents after the age of 40 years. It is the tumour most likely to have metastasized to a regional lymph node by the time of presentation. Malignant melanoma metastasizes via the lymphatics to lymph nodes and via the bloodstream to the brain, lung, liver, bones and skin.

Provided the diagnosis is made early enough, the prognosis may be good. Massive public education programmes initiated in Australia (spearheaded by Queensland) and elsewhere have reinforced this.

The late Alexander Breslow, a pathologist, showed an inverse relationship between tumour thickness and survival: the more superficial the lesion at the time of excision, the better the prognosis. The Breslow thickness is measured in millimetres from the granular cell layer of the epidermis to the deepest tumour cells in the dermis. He showed 100% survival in tumours less than 0.76 mm, but only 50% 5-year survival in those greater than 3.5 mm thick. Similarly, Clark related survival to depth of infiltration of the dermis. He described five levels:

1. Confined to the epidermis (in situ)
2. Infiltration of the papillary dermis
3. Infiltration to the junction of the papillary with the reticular dermis
4. Infiltration of the reticular dermis
5. Infiltration of the subcutaneous fat

He showed that levels 1 and 2 have a good prognosis, and that 3–5 have an increasingly poor one. Other poor pathological prognostic indicators are ulceration, lymphovascular invasion and regression of the primary.

It has become clear that the growth characteristics, and hence prognosis, of the different types of melanoma vary. Lentigo maligna evolves very slowly, superficial spreading melanomas less so and nodular melanomas rapidly. Lentigo maligna, superficial spreading and acral lentiginous melanoma spread horizontally initially and only subsequently invade vertically. Therefore, the prognosis is excellent in lentigo maligna, which remains in situ for many years, and in the superficial spreading malignant melanoma during its horizontal spreading phase before vertical invasion occurs. In contrast, the nodular malignant melanoma, which has no horizontal phase but grows vertically from the start, has a much poorer outlook. Prognosis is also determined by the site of the lesion, being much worse on the back (possibly because it is less visible) than on the leg. Females fare better than males. The overall survival for malignant melanoma diagnosed in pregnancy is similar to that of non-pregnant women of the same age after adjustment for Breslow thickness. Subsequent pregnancies do not affect prognosis.

Most malignant melanomas develop de novo in skin that was previously normal. However about 20% can be shown histologically to be associated with a pre-existent naevus (although this does not always correlate well with the patient's recollection of such a mole). The possession of many moles is a risk factor for malignant melanoma, but this may be an indication of how much solar exposure the individual has had: there is a clear latitude gradient in Australia in that Queenslanders have many more naevi than those in New South Wales, who in turn have more than those in Tasmania. As most Caucasians have 20 or more moles, prophylactic removal is not warranted, practical or cosmetically acceptable. There are however certain types of mole that may predispose to melanoma:

- bathing trunk naevus syndrome (see above)
- congenital melanocytic naevi (see above and Fig. 11.42)
- atypical mole syndrome, also known as familial atypical mole malignant melanoma syndrome (FAMMM) or dysplastic naevus syndrome.

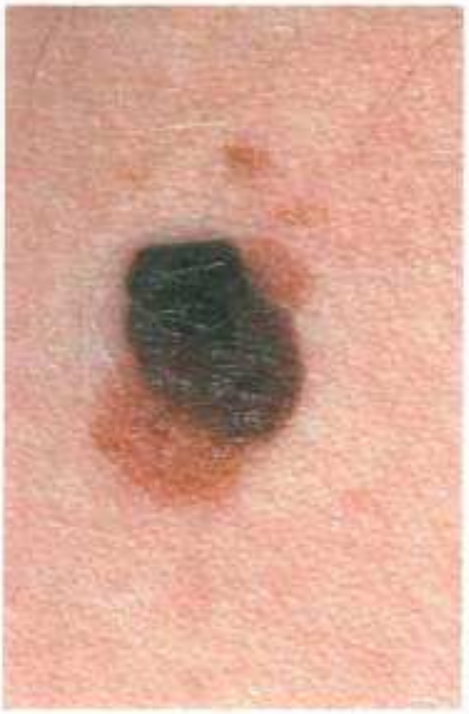


Fig. 11.42 Malignant melanoma developing in a congenital naevus. A light brown larger mole had been present all her life. She noted the dark brown and black colours and change in shape when she was 43.

ATYPICAL MOLE SYNDROME

A syndrome of many clinically atypical moles some of which are larger than normal and have a histologically distinctive appearance occurring in a sporadical familal setting, which may be a risk factor for malignant melanoma.

Aetiology

Patients have large numbers of moles, some of which are atypical (Fig. 11.43). One hundred naevi (Figs 11.44 and 11.45) larger than 0.2 mm in diameter (greater than 50 in children and adolescents or after the age of 50) associated with large atypical moles between 1 and 2 cm in size should raise suspicion of the syndrome. Two or more of the moles should have a dysplastic histology for the diagnosis to be made. These naevi are very sensitive to solar irradation. Patients and their families are at increased risk of developing malignant melanoma including of the eye. Unfortunately this fairly straightforward concept of a clinically abnormal phenotype of large atypical moles associated with a familial tendency to melanoma has evolved to such an extent that a single large atypical naevus without a family setting is included in the discussion. The risk for melanoma in this latter group of patients is essentially undetermined but it is considered wise that they should be removed. Patients who are particularly at risk are those with a personal and/or family history of malignant melanoma. Patients with the dysplastic naevus syndrome should scrupulously avoid solar exposure and have their skin examined on a regular basis.

Clinical Features

Symptoms

Many moles.

Morphology

The atypical features are slightly irregular margins and pigmentation. These moles are not obviously malignant melanomas but they are not quite as regular as ordinary moles.

Distribution

Anywhere on the body including unusual sites such as the scalp and buttocks.

Histopathology

There is a distinctive pattern of melanocytic proliferation within the epidermis (atypical lentiginous melanocytic hyperplasia) that is different from the pattern of nests of melanocytes associated with compound or junctional naevi. There is an associated stromal response. They may be divided into lentiginous and epithelioid variants. The former, which is more common, is typified by basally located melanocytes that show nuclear pleomorphism, hyperchromatism and a conspicuous pericellular retraction halo (Fig. 11.46). The epidermal ridge pattern is accentuated as in a lentigo. A characteristic finding is desmoplasia within the papillary dermis, which follows the lower borders of the epidermal ridges. The latter is composed of larger cells with eosinophilic cytoplasm that contains fine granular melanin pigment, vesicular nuclei and sometimes prominent nucleoli. In both variants, a lymphocytic response is present in the superficial dermis. All dysplastic naevi should be carefully sectioned to exclude focal development of invasive (usually superficial spreading) malignant melanoma.

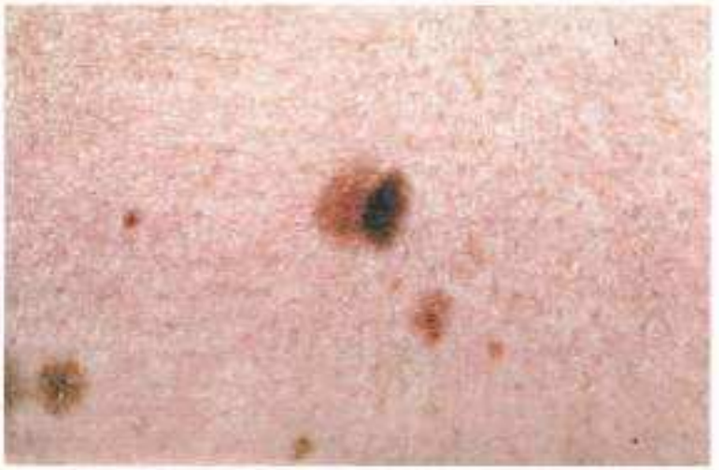


Fig. 11.43 Dysplastic naevus. The central mole has a dark oval component to the right side of the lesion, which contrasts with the other regular benign moles. Such moles, although benign, should be excised for pathological confirmation and because they may transform.

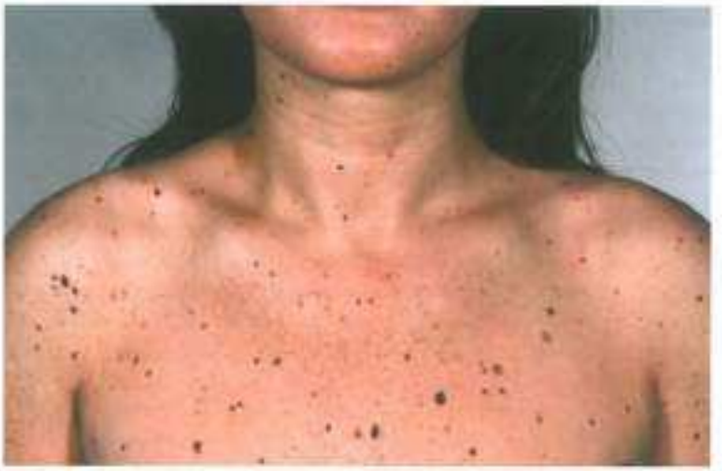


Fig. 11.44 Atypical (dysplastic) mole syndrome. There are a multitude of dark moles of various shapes and sizes to be seen. There may be a family history and there is an increased risk of malignant transformation.

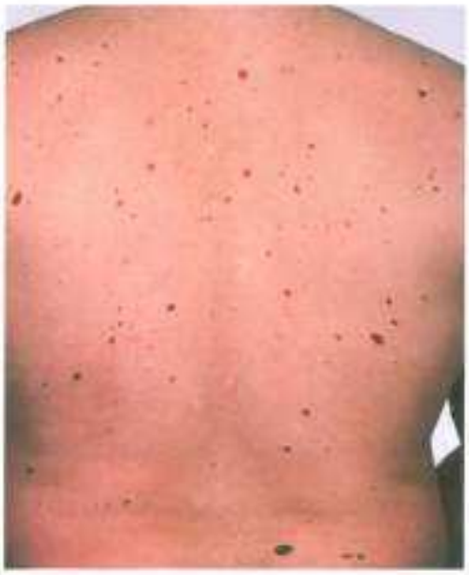


Fig. 11.45 Atypical (dysplastic) naevus syndrome. There are many more moles than usual, producing a striking appearance. Many are very dark and some are quite large.

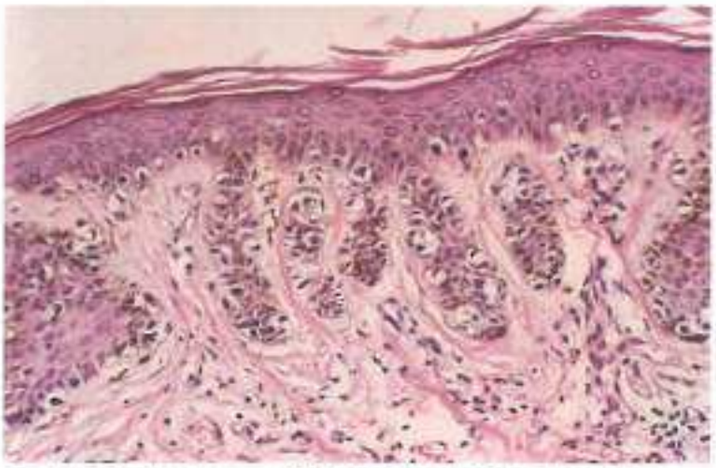


Fig. 11.46 Dysplastic naevus. Note the epidermal lentiginous hyperplasia and atypical melanocytes aligned along the sides of the ridges in addition to occupying the tips. The nuclei are irregular and hyperchromatic. Papillary dermal fibrosis is evident.

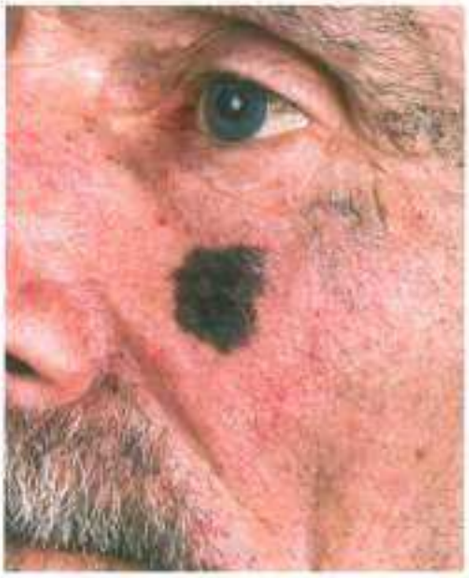


Fig. 11.47 Lentigo maligna. Hutchinson's or Dubreuilh's lentigo is a melanoma in situ which is normally on the face of an older sun-damaged individual. Note the scalloped notched margin.

Subtypes of cutaneous malignant melanoma

LENTIGO MALIGNA MELANOMA

Clinical Features

Symptoms

A mark on the face.

Morphology

It appears as a flat, pigmented lesion that gradually enlarges. This initial horizontal growth phase is slow and it is known as *lentigo maligna* or Hutchinson's freckle (described in 1890) and Dubreuilh lentigo malin des vieillards (described in 1894). The colours within the lesion vary from light tan to brown or black (Fig. 11.47), sometimes with patches of red, blue, grey or white. The margin is irregular and may be notched or indented. There are usually signs of chronic solar damage around the lesion. They are often quite large when the patient presents (Fig. 11.48). Eventually, when invasion through the basement membrane into the dermis occurs, part of the lesion becomes thickened and eventually nodular (Fig. 11.49). It is then known as *lentigo maligna melanoma*. Very

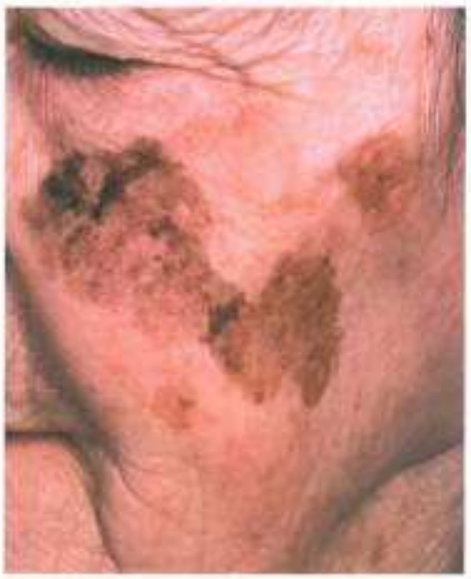


Fig. 11.48 Lentigo maligna. The lesion is made up of various colours and has an irregular indented margin. It grows slowly and may attain a large size before presentation.

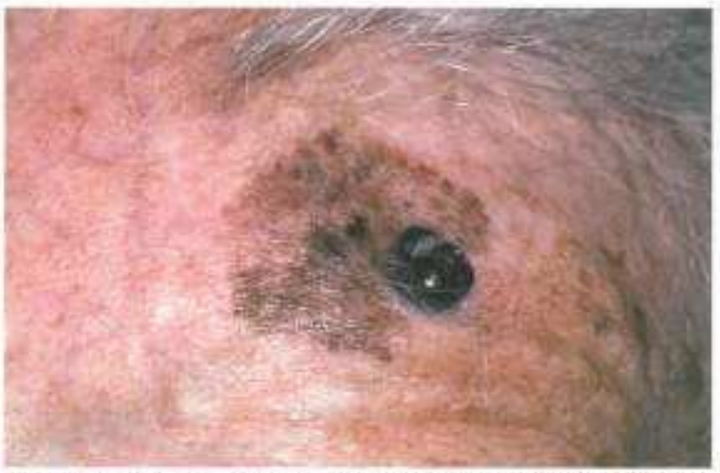


Fig. 11.49 Lentigo maligna melanoma. Eventually invasion occurs and part of the lesion becomes thickened and, in this case, nodular.

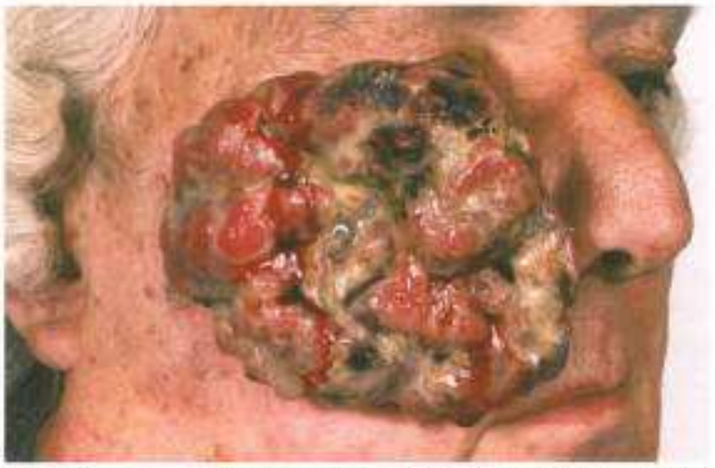


Fig. 11.50 Lentigo maligna melanoma. Very rarely, in neglected cases, nodules may develop and metastasis may occur, as in this nonagenarian.

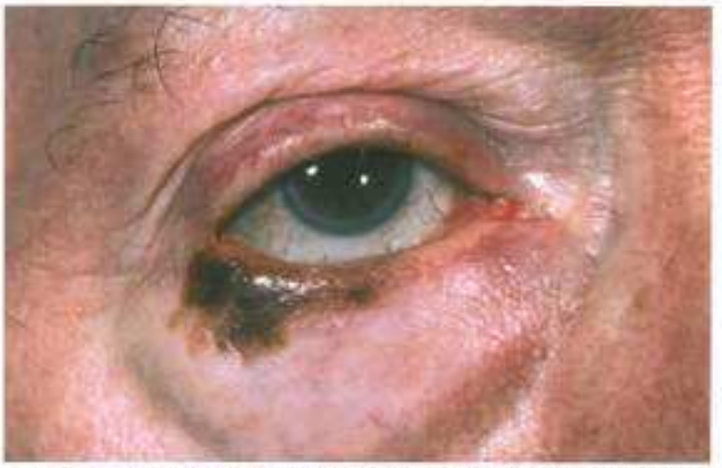


Fig. 11.51 Lentigo maligna. The management of this condition is complicated either because of its size or site. Imiquimod topically is helpful in lesions confined to the epidermis.

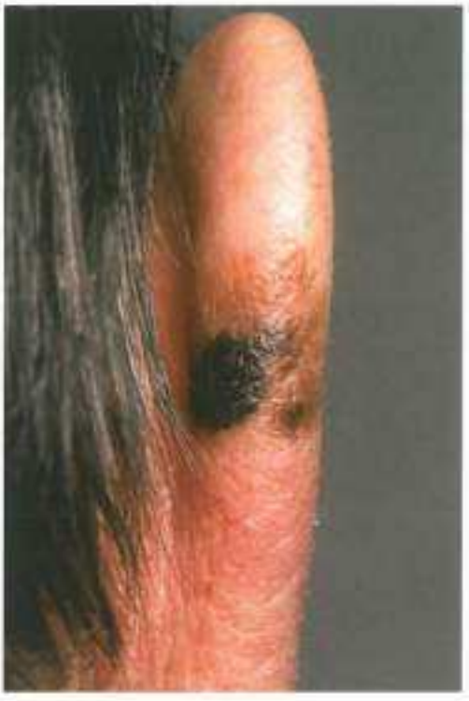


Fig. 11.52 Lentigo maligna. These lesions occur in the elderly in the head and neck region. Note the irregularity of outline and pigmentation on this man's ear.

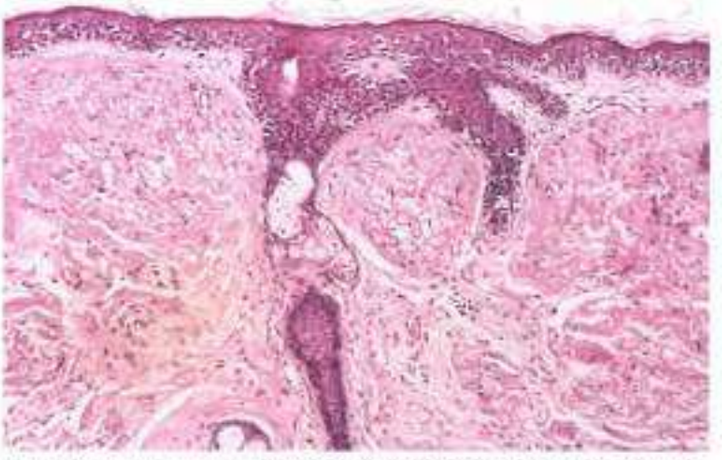


Fig. 11.53 Lentigo maligna. Atypical melanocytes with irregular, hyperchromatic nuclei are present along the basal layers of the epidermis. Follicular involvement is characteristic and solar elastosis is prominent.

rarely, in neglected cases, deep invasion occurs with multiple nodule formation (Fig. 11.50).

Distribution

The face (usually the cheeks, nose, temple, forehead or eyelid – Fig. 11.51), but occasionally the neck, or ear (Fig. 11.52) of an older person.

Histopathology

Lentigo maligna is invariably accompanied by features of actinic damage (epidermal atrophy and solar elastosis). An established lesion is characterized by proliferation of atypical melanocytes predominantly along the basal layer of the epidermis (Fig. 11.53). These cells have irregular hyperchromatic nuclei and characteristically show marked cytoplasmic vacuolation. They involve the basal layers of hair follicles. Pigmentation is variable but in most instances is markedly increased, involving adjacent keratinocytes, dermal macrophages (melanophages) and sometimes the keratin lamellae of the stratum corneum. As the lesion progresses, clusters of atypical cells gather at the dermo-epidermal junction, often adopting a spindle cell form. Invasion is typically multifocal and the resultant tumour, lentigo maligna melanoma, most often has a spindle cell pattern.

INTRAEPIDERMAL MALIGNANT MELANOMA

Clinical Features

Symptoms

A mole that is growing or changing colour.

Morphology

A flat, very dark macule (Fig. 11.54) which may spread radially and resemble a superficial spreading melanoma with variable pigmentation and an irregular outline (Fig. 11.55) or become a papular and later a nodular melanoma.

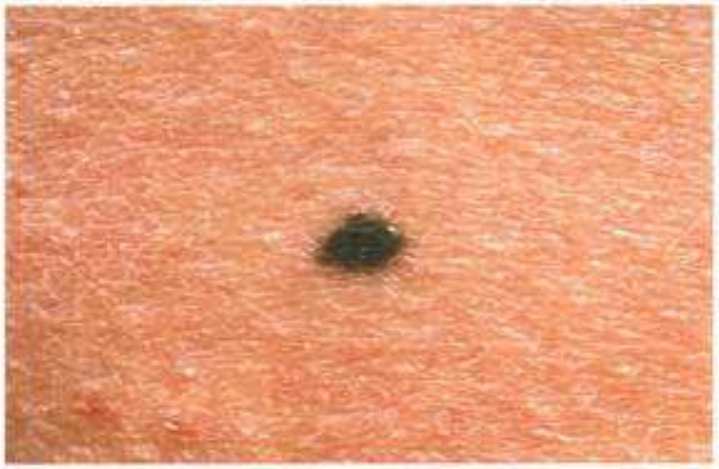


Fig. 11.54 Melanoma in situ. It starts as a very dark macule. It may spread radially or vertically becoming papular. Public education campaigns have been so effective that many patients present with early lesions confined to the epidermis.

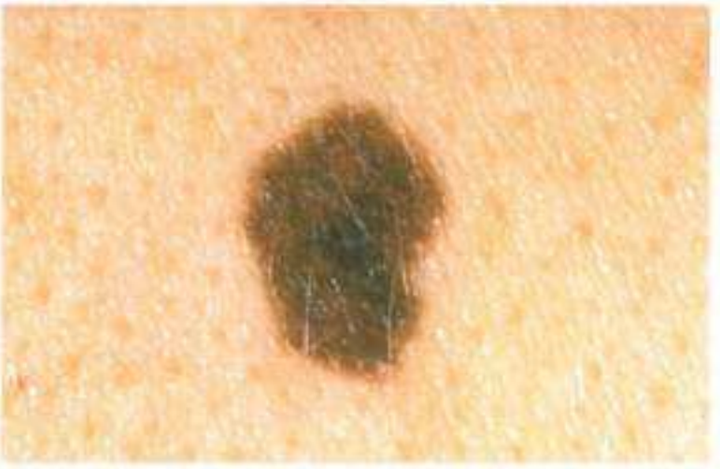


Fig. 11.55 Melanoma in situ. If it spreads radially, it is similar clinically to a superficial spreading melanoma with uneven pigmentation and irregular notched edges but it is quite flat. The prognosis is excellent.

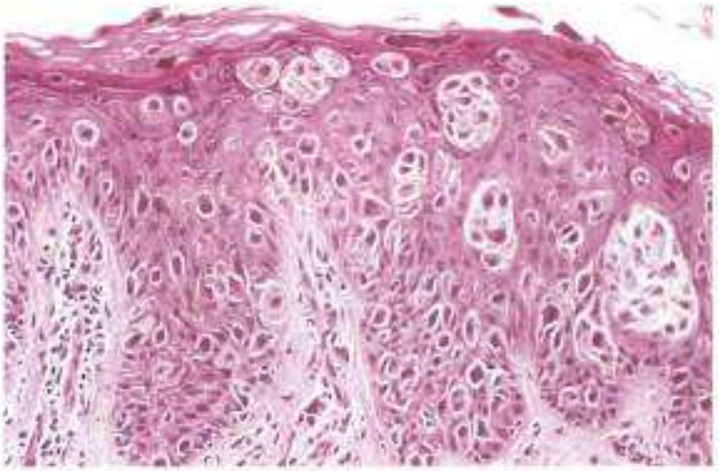


Fig. 11.56 Melanoma in situ. Clusters of 'Pagetoid' melanocytes are widely distributed at all layers of the epidermis (so-called 'buckshot scatter'). This is Clark's level 1.

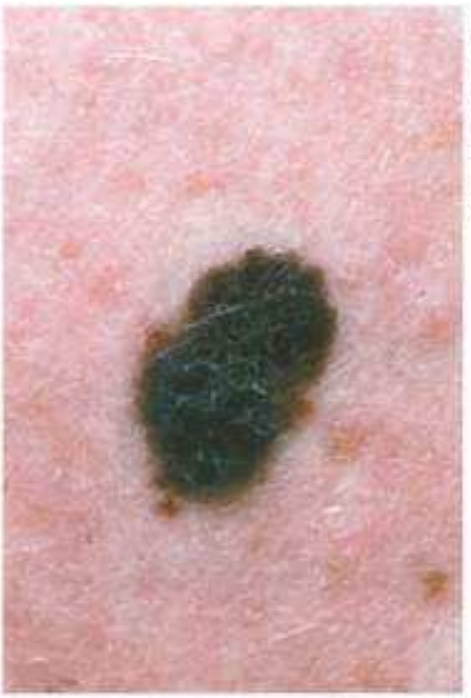


Fig. 11.57 Superficial spreading malignant melanoma. The lesion is very dark in colour, a classic example. There is brown pigmentation at the margin, an irregular edge and faint white halo to be seen.

Distribution

Anywhere, but particularly on the limbs and torso. It differs from lentigo maligna, which is also an in situ form of melanoma, in that it occurs in much younger individuals, is not restricted to the face and is not associated with gross solar damage or elastosis.

Histopathology

Atypical enlarged melanocytes with abundant pale cytoplasm and hyperchromatic nuclei are scattered in a 'buckshot' pattern through the hyperplastic epidermis (Fig. 11.56). There is no invasion or solar elastosis.

SUPERFICIAL SPREADING MALIGNANT MELANOMA

Clinical Features

Symptoms

A mole that is enlarging and changing colour.

Morphology

It begins as a flat patch of pigmentation that becomes just palpable (Fig. 11.57). It spreads out laterally and horizontally and has an irregular outline, often notched and indented (Fig. 11.58). The skin creases are

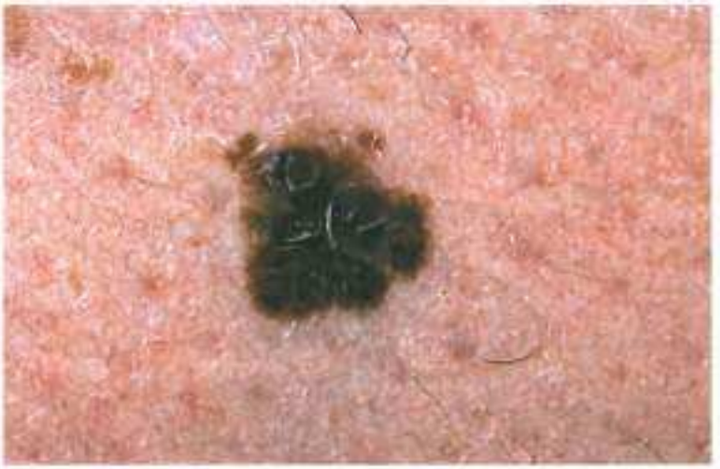


Fig. 11.58 Superficial spreading malignant melanoma. It is more common in young women and occurs particularly on a limb, especially the leg. The back is the commonest site in males.

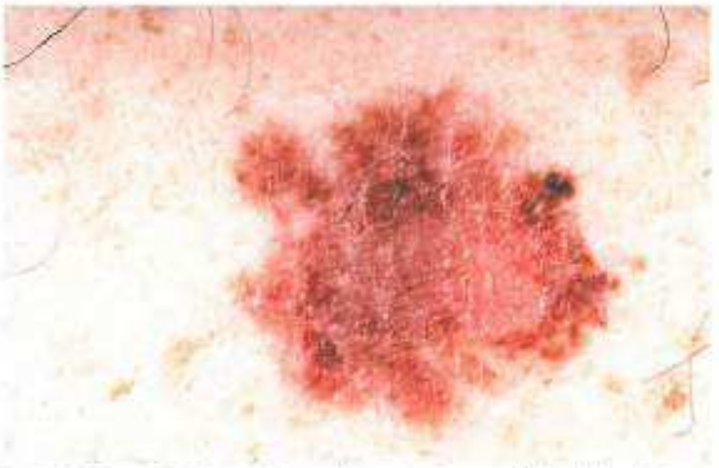


Fig. 11.59 Superficial spreading malignant melanoma. Although these lesions are usually predominantly dark brown or black, they may be quite brown but it is the variable shades of pigment and the irregular edge that gives away the diagnosis.

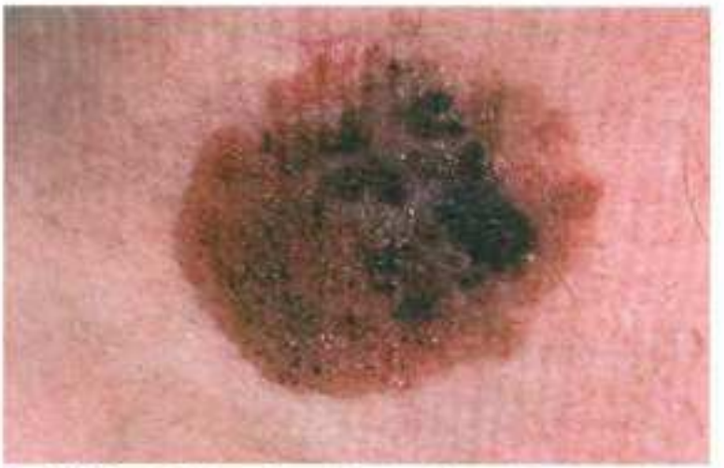


Fig. 11.60 Superficial spreading malignant melanoma. This brown mole has been present on the dorsum of his foot all his life. The dark areas developed subsequently. He was 16, which is unusually young for a malignant melanoma.

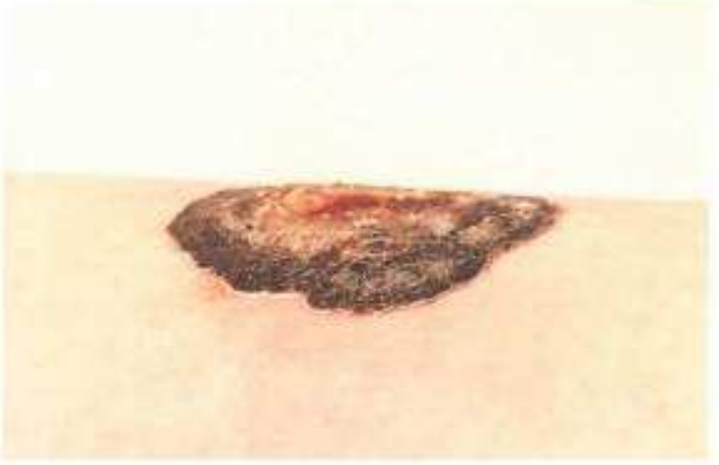


Fig. 11.61 Superficial spreading melanoma. Initially the lesion spreads horizontally. This is known as the radial growth phase when the prognosis is good.

Fig. 11.62 Superficial spreading malignant melanoma. Following the horizontal spreading phase, the lesion commences its vertical growth phase and thickens to become a plaque or nodule.

present initially but gradually disappear. There are various shades of brown (Fig. 11.59), admixed with black (Fig. 11.60), and sometimes foci of red, blue and purple. The prognosis is excellent during this horizontal growth phase (Fig. 11.61) but diminishes as the lesion thickens (Fig. 11.62) and becomes nodular (Fig. 11.63).

Distribution

It is most common on the legs in females and on the trunk in males but it can occur anywhere on the body. They are seen mostly in the young and middle-aged, with females predominating. Some believe that recreational patterns of sun exposure are responsible for the distribution. It may arise de novo or from a dysplastic or congenital naevus.

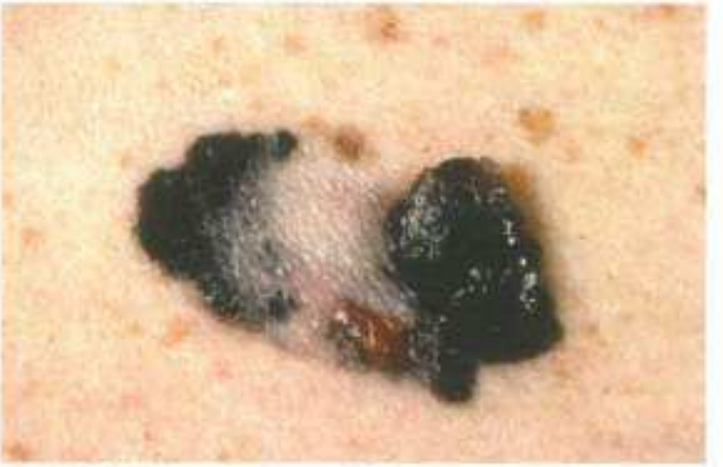


Fig. 11.63 Vertical invasion in a superficial spreading melanoma. A nodule has developed on the right side. The grey area represents regression of the melanoma. It was on his back and he presented late. He died 3 years later.

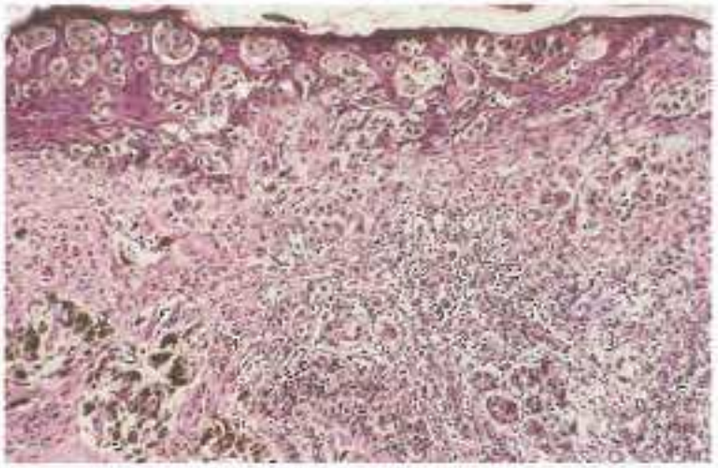


Fig. 11.64 Superficial spreading malignant melanoma. Pleomorphic melanocytes are scattered within the epidermis and infiltrated the superficial dermis. Note the heavy chronic inflammatory cell infiltrate.

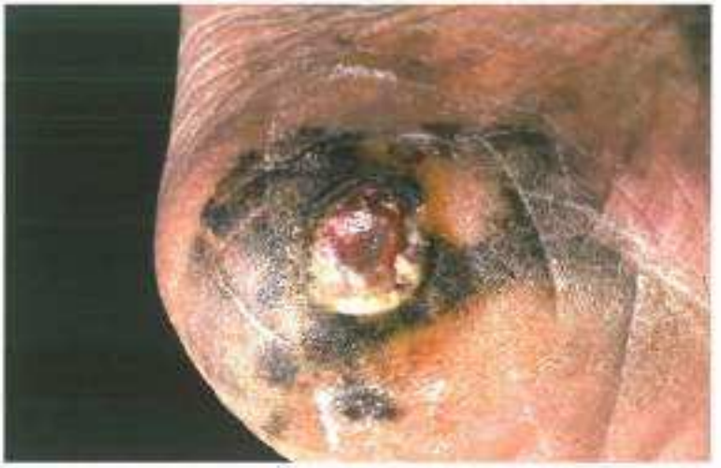


Fig. 11.65 Acral lentiginous malignant melanoma. A nodule has occurred within a flat area of pigmentary variation and irregular outline. The sole of the foot is the classic site for this tumour.

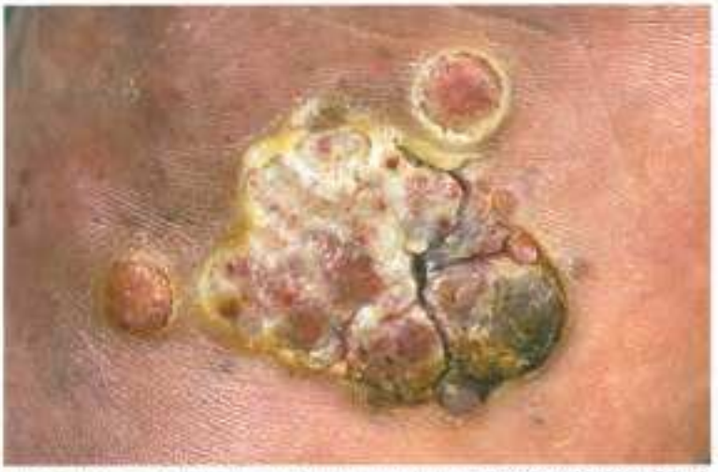


Fig. 11.66 Acral lentiginous malignant melanoma. These lesions may present late because they are not noticed. This one has become amelanotic, but the patient recalled having a mole on his foot.

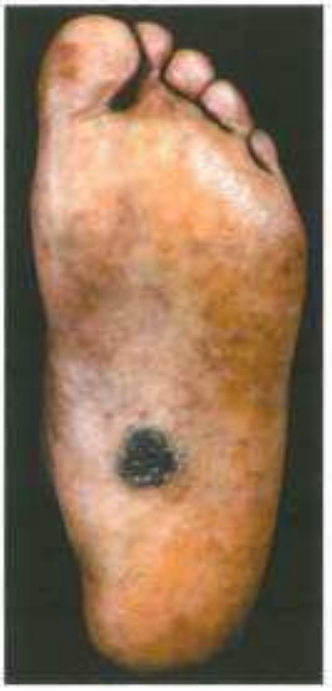


Fig. 11.67 Acral lentiginous malignant melanoma. These lesions are commonest in Orientals and Africans but are the rarest of the melanomas.

Histopathology

In contrast to lentigo maligna melanoma, superficial spreading malignant melanoma is not usually associated with features of severe actinic damage. Abnormal cells are irregularly distributed throughout the epidermis, singly or in clusters, and often involve the upper layers in a pattern reminiscent of Paget's disease, hence its alternative designation of *Pagetoid melanoma*. The cells are large with abundant cytoplasm, pleomorphic vesicular nuclei (Fig. 11.64) and prominent eosinophilic nucleoli. Pigmentation is variable but is often marked. Tumour cells characteristically spread from one epidermal ridge to the adjacent one. Invasion occurs and the infiltrating tumour is usually of the epithelioid cell type.

ACRAL LENTIGINOUS MALIGNANT MELANOMA

Clinical Features

Symptoms

It appears as an irregular pigmentation on the palms or soles, sometimes arising from a naevus.

Morphology

Similar initially to lentigo maligna and superficial spreading malignant melanoma, but invasion with nodule formation (Figs 11.65 and 11.66) and metastasis occur early.

Distribution

The sole (where it may not be noticed and diagnosed late when a bleeding nodule forms; Fig. 11.67) or on the palm. This is the rarest form of melanoma in Caucasians, but commonest in Africans and Orientals.

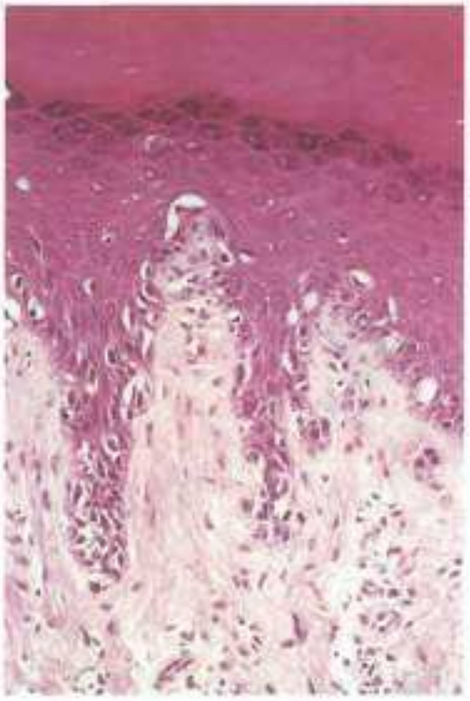


Fig. 11.68 Acral lentiginous malignant melanoma. The epidermal ridge pattern is prominent. The basally located atypical melanocytes show conspicuous vacuolation. There is dermal fibrosis in this lesion on the sole.

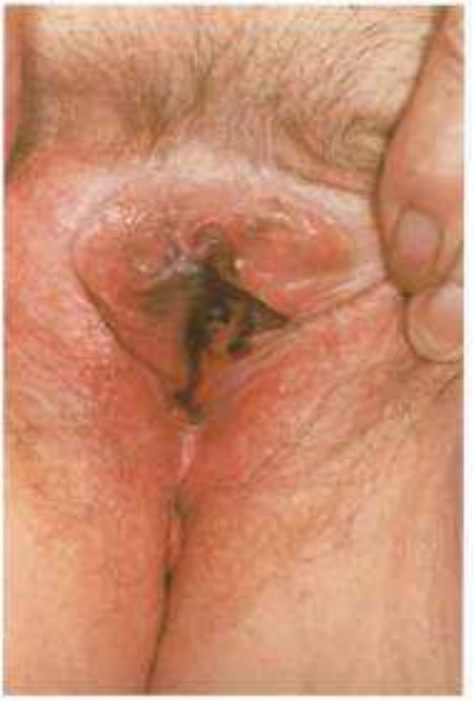


Fig. 11.69 Mucosal melanoma. The pigmentation is very dark and irregular in outline. These genital melanomas are very unusual. (Courtesy of Dr Pamela Todd.)

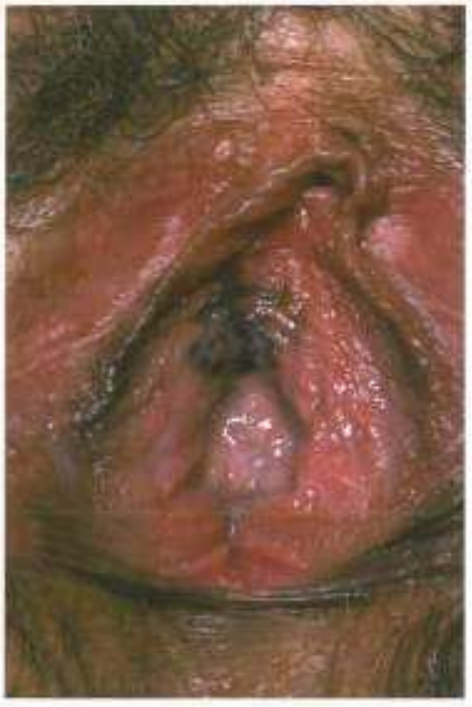


Fig. 11.70 Vulval melanotic macule. Pigmented macules may occur on the genitalia. Biopsy is necessary to distinguish this benign lesion from a malignant melanoma. (Courtesy of Dr Elisabeth Higgins.)

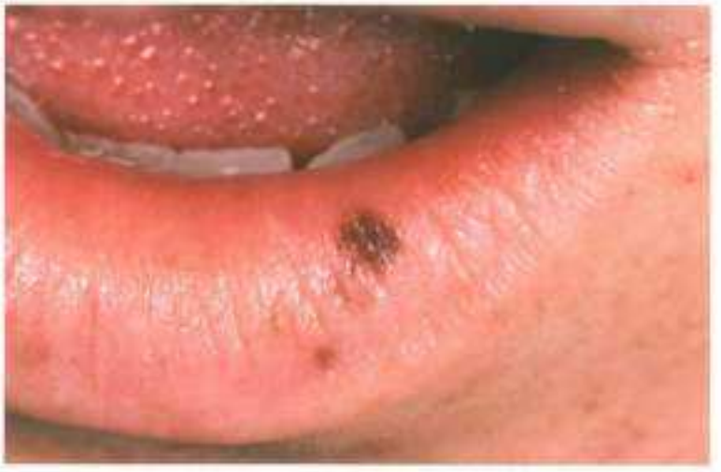


Fig. 11.71 Benign labial macule. Malignant melanoma of the oral cavity or lip is rare. Benign labial macules are common. However, they are often excised for histological confirmation.

Histopathology

The features are similar to those of lentigo maligna except that the epidermis is hyperplastic. The most common variant is characterized by atypical melanocytes situated predominantly along the basal aspect of the epidermis, although the higher reaches, including the stratum corneum, may also be involved. Individual cells are pleomorphic with hyperchromatic nuclei and conspicuous nucleoli (Fig. 11.68). Mitotic figures are frequent. Nest formation with both epithelioid and spindle cell forms is common. The invasive stage is usually of the spindle cell type. A Pagetoid variant is occasionally seen.

MUCOSAL MELANOMA

Clinical Features

Symptoms

An irregular patch of pigmentation in the mouth, around the anus or on the genitalia.

Morphology

The pigmentation is irregular in outline and in density of colour.

Distribution

These melanomas are rare but occur in the oral cavity, around the anus and on the genitalia (Fig. 11.69). Benign melanotic macules of the genitalia (Fig. 11.70) or lip (Fig. 11.71) may cause diagnostic confusion.

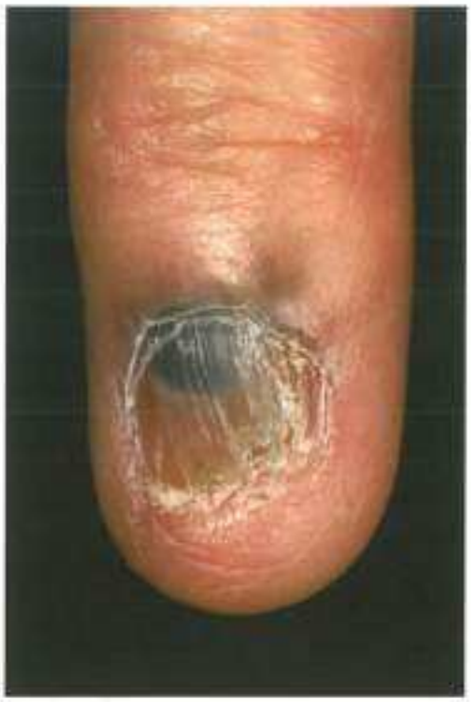


Fig. 11.72 Subungual melanoma. There is pigmentation under the nail and also on the skin of the posterior nailfold. The nail plate itself is split and distorted by the tumour underneath.

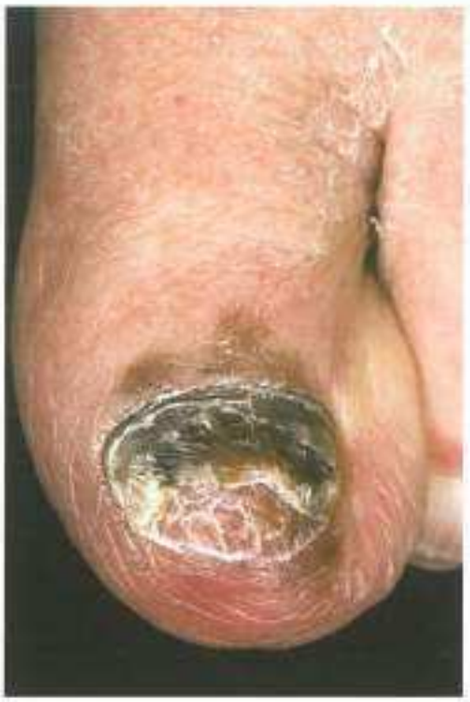


Fig. 11.73 Subungual melanoma. There is pigmentation of the nailfold, of the nail plate and around the fingertip. There is a reddish tumour at the distal end of the nailbed. Amputation of the digit is the treatment of choice.

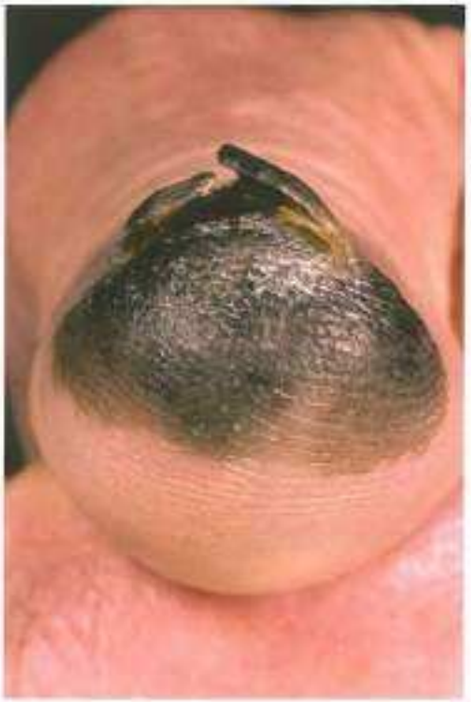


Fig 11.74 Subungual melanoma. There is considerable pigmentary involvement of the surrounding skin (Hutchinson's sign) and a tumour under the nail which has caused a split in the the nail plate.

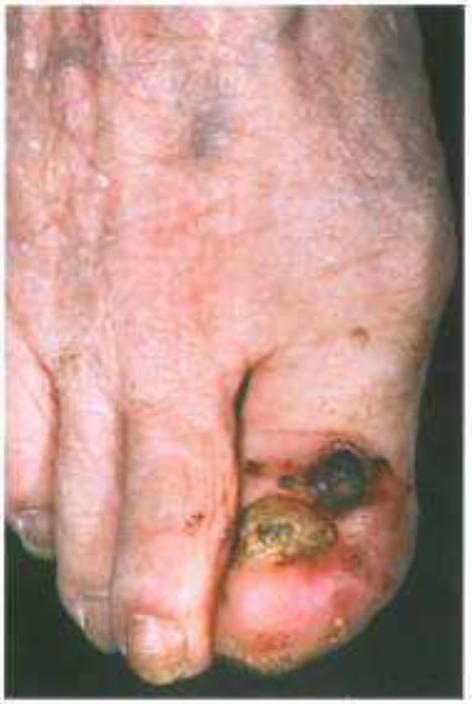


Fig. 11.75 Subungual malignant melanoma. The big toe is the most common nail to be affected. The nail is thickened and distorted. There is pigmentation around the nail and a black tumorous nodule to the medial side of the base of the nail.

SUBUNGUAL MELANOMA

Clinical Features

Symptoms

Pigmentation under a nail, which may be mistaken for an injury.

Morphology

The nail is deeply pigmented, often with irregular shades (Fig. 11.72). There is usually a flat, irregular, pigmented patch on the skin of the nail folds (Hutchinson's sign) (Fig. 11.73). The nail does not grow properly, becomes distorted and splits as the tumour thickens (Figs 11.74 and 11.75).

Histopathology

There is lentiginous spread of pleomorphic, often dendritic, atypical melanocytes in the basal and suprabasal layers. The dermal melanoma cells are pleomorphic.

Distribution

The melanoma occurs under any nail.

Differential Diagnosis

- **Trauma** The patient may recall this. Paring the nail away with a scalpel blade may reveal flecks of blood in the nail plate (Fig. 11.76) and it may be possible to remove the blood altogether.
- **Linear melanonychia** This is very common in black-skinned patients (Fig. 11.77) but is unusual in Caucasians. The line is irregular in melanoma (Fig. 11.78).

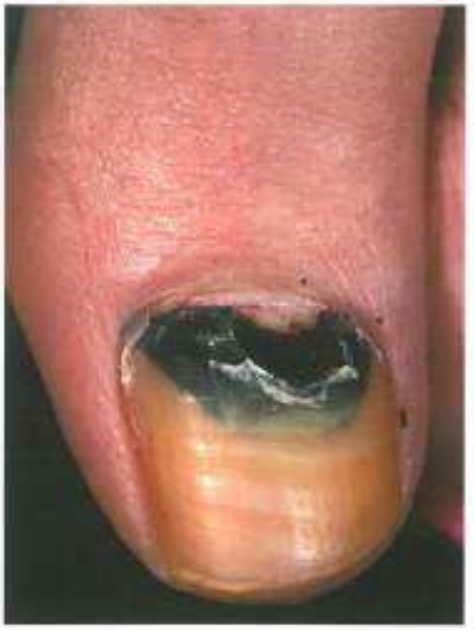


Fig. 11.76 Haemorrhage under the nail. The area is black but surrounded by the red-brown, russet coloured pigmentation of altered blood.

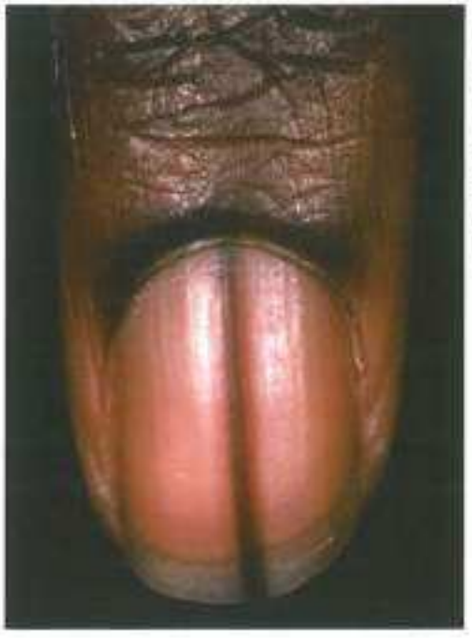


Fig. 11.77 Linear melanonychia. The line is quite straight and evenly pigmented. It is very common in black-skinned races and is always benign. It does occur in Caucasians but not often, and a biopsy may be wise if there is doubt.

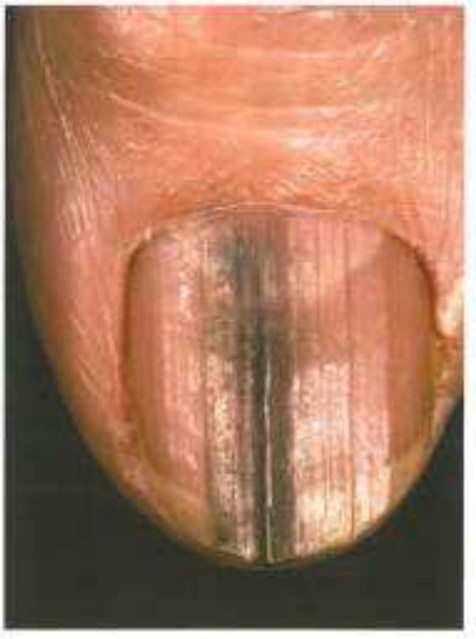


Fig. 11.78 Subungual melanoma. This in situ lesion may start as a line of pigmentation but it is irregular in outline and degree of colour.

PAPULAR AND NODULAR MALIGNANT MELANOMA

Clinical Features

Symptoms

Both present as growth of a mole. Nodular malignant melanoma may bleed latterly.

Morphology

There is a papule which is very dark (Fig. 11.79) or black (Fig. 11.80) but occasionally brown or flesh-coloured (amelanotic) with a rim of pigment at one side (Fig. 11.81). The outline is not particularly irregular. Gradually it becomes a nodule (Figs 11.82 and 11.83), which may bleed, ulcerate and metastasize (Fig. 11.84). Occasionally, the lesion has a surrounding halo (Fig. 11.85). Amelanotic tumours are not easy to diagnose, being purple or red-brown with little pigmentary change.

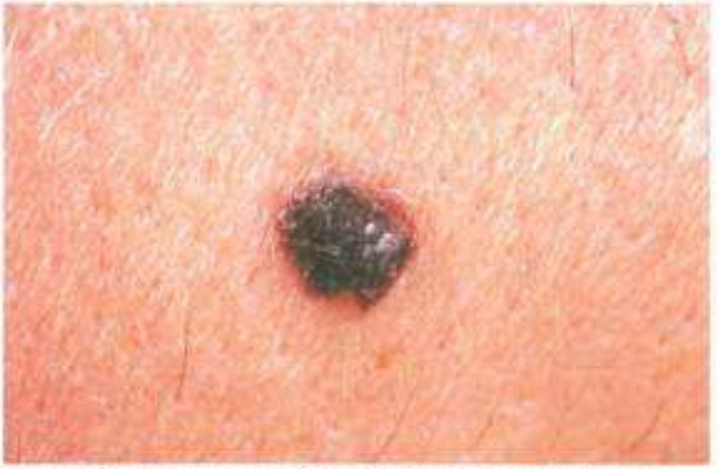


Fig. 11.79 Papular melanoma. This small papule is predominantly a uniform dark brown colour bordering on black but there is a brown area to one side, which would point to the diagnosis of malignant melanoma.

Fig. 11.80 Papular malignant melanoma. The lesion is uniformly deeply pigmented with an irregular spur at 3 o'clock. It was 0.6 cm in size. These lesions invade vertically *ab initio* and are liable to be aggressive if not diagnosed early.

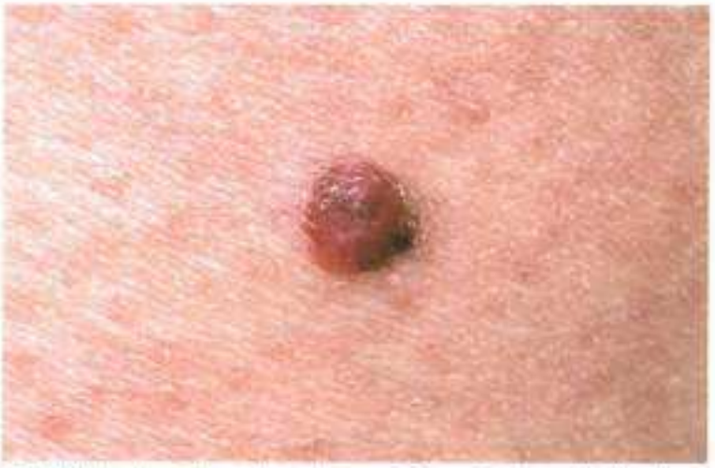


Fig. 11.81 Amelanotic papular melanoma. This papule is brown but the tiny black area to one side might suggest the correct diagnosis.

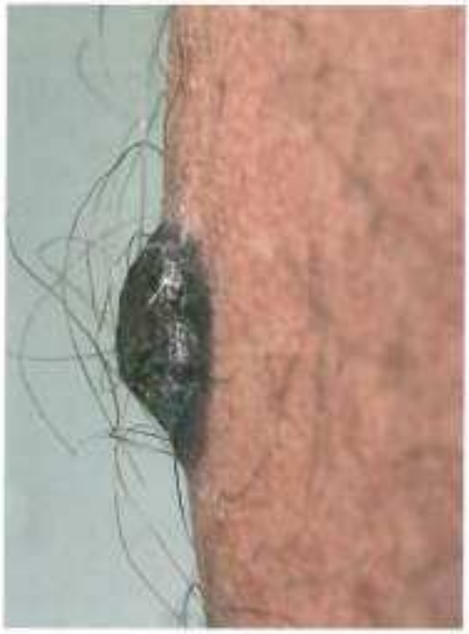


Fig. 11.82 Nodular malignant melanoma. This nodule was 2.9 mm Breslow thickness and the skin lymphatics were involved histologically.

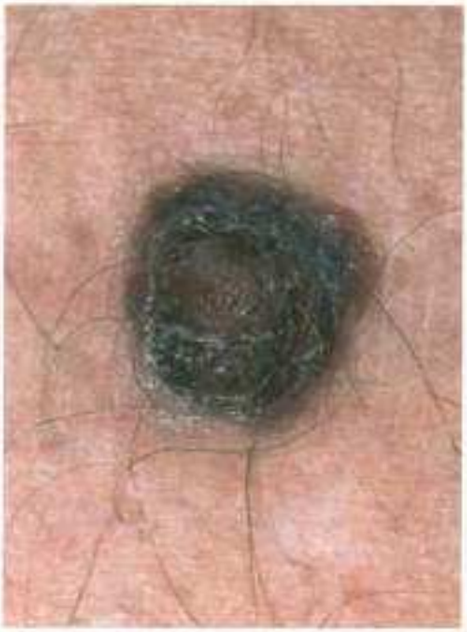


Fig. 11.83 Nodular malignant melanoma. This nodule (also depicted in Fig. 11.82) was eroded on its surface and had bled, which augurs a poor prognosis.

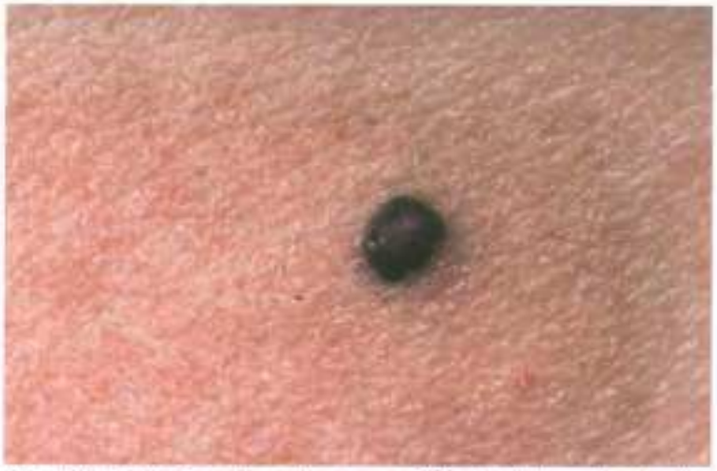


Fig. 11.84 Metastatic malignant melanoma. This metastasis developed within one year of the excision of the nodule in Figs 11.82 and 11.83.

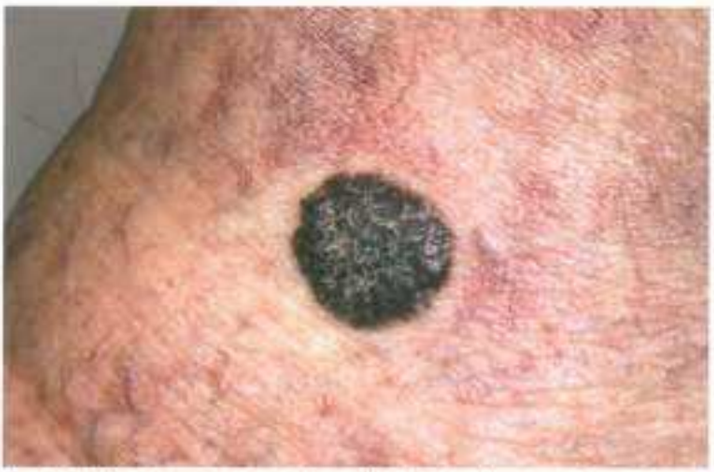


Fig. 11.85 Nodular melanoma. The nodule is black with an irregular outline and slight pale halo. This lesion was present on the leg, the commonest site in women.

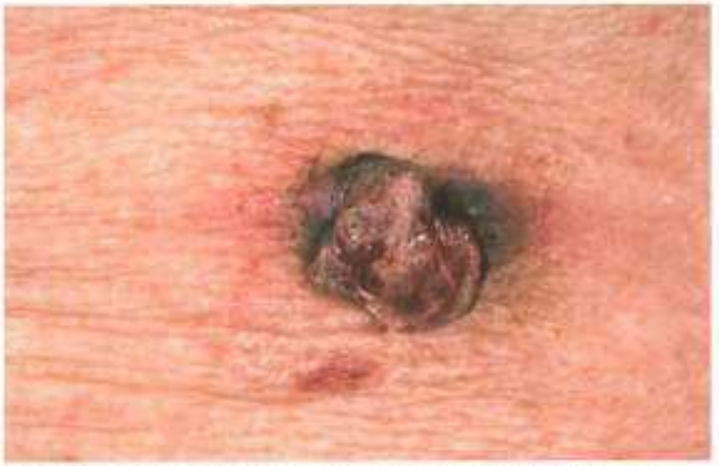


Fig. 11.86 Amelanotic melanoma. A cursory examination might reveal a red friable lesion and be mistaken for a pyogenic granuloma but the pigmentation at the periphery is the clue to the real diagnosis.

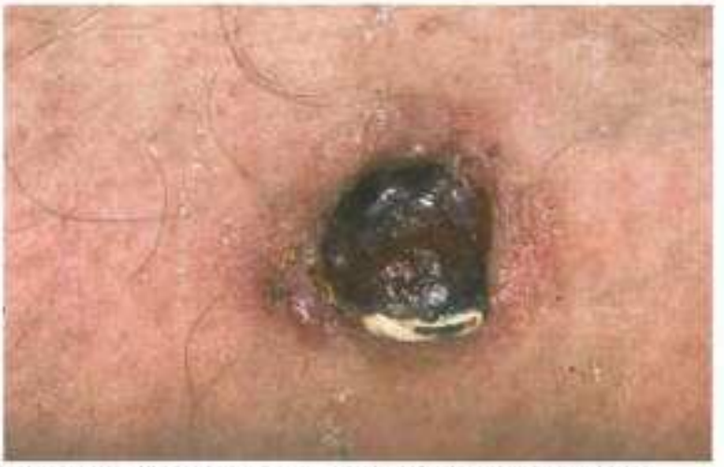


Fig. 11.87 Amelanotic melanoma. This nodule is dark red with an eroded surface, and might resemble a haemangioma, but there is melanin pigmentation at the top of the lesion and it was malignant.

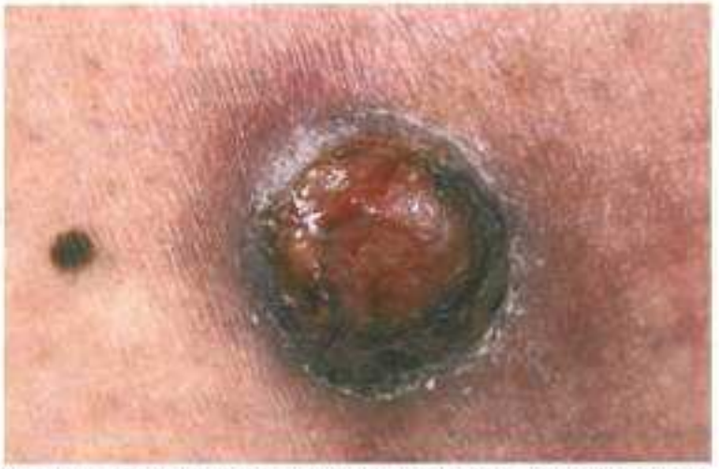


Fig. 11.88 Amelanotic melanoma. This patient presented with this bleeding red tumour with a pigmented rim on the back of her calf. Although it metastasized both to the skin locally and to the inguinal lymph nodes within a year of excision, she is in complete remission 20 years later.

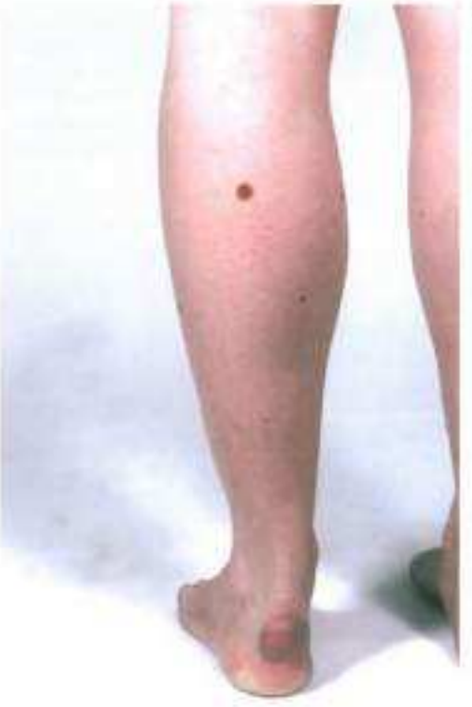


Fig. 11.89 Malignant melanoma.
The commonest site for a malignant melanoma (in this case a papular one) in the female is on the limb, particularly the leg.

although usually there is a tell-tale narrow rim of brown (Figs 11.86–11.88) to one side of the lesion.

Distribution

Papular and nodular melanoma can occur anywhere, but particularly on the limbs (females) (Fig. 11.89) or trunk (males).

Histopathology

It has no horizontal growth phase, unlike the other subtypes. It invades vertically ab initio (Fig. 11.90). The histology, however, of invasive vertical growth phase melanoma is similar whatever type it originates from.

There is junctional activity (Fig. 11.91) and varying proportions of epidermal and dermal infiltration. Pleomorphic tumour cells infiltrate the epidermis (which may often be ulcerated) and extend to a varying degree into the dermis. Although traditionally classified into epithelioid and spindle cell types (the former most often associated with superficial spreading and nodular variants and the latter with lentigo maligna melanoma and acral lentiginous melanoma), many tumours are mixed.

Epithelioid cells have abundant cytoplasm and large nuclei with eosinophilic nucleoli. The spindle cell form, particularly in amelanotic variants, may be confused with other spindle cell tumours if an origin from the epidermis is not recognized. In such instances, the use of a Masson–

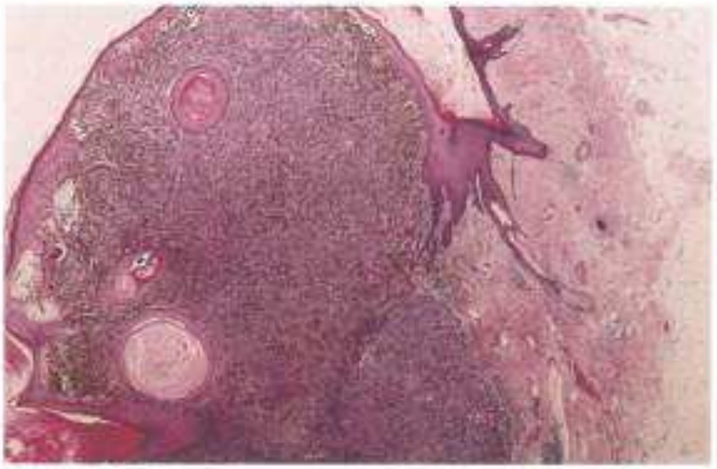


Fig. 11.90 Nodular malignant melanoma. The epidermis is elevated into a pedunculated nodule by this heavily pigmented tumour. Superficial horn cysts have been formed by squamous epithelial proliferation.

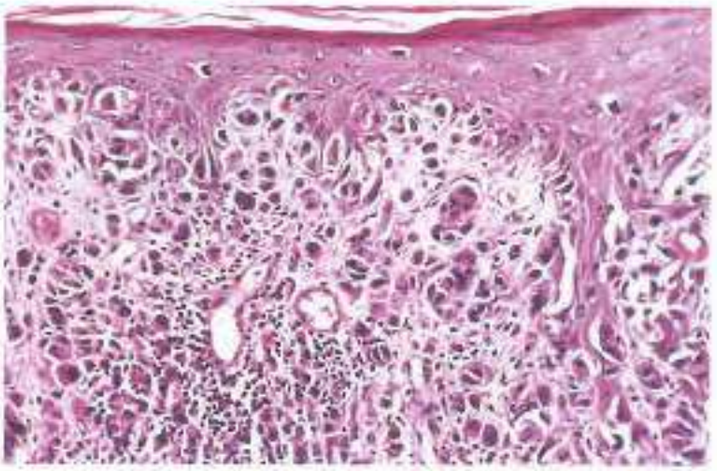


Fig. 11.91 Nodular melanoma. Conspicuous junctional activity is present. Epithelioid cells predominate with abundant pink cytoplasm and vesicular nuclei often containing darkly staining nucleoli.

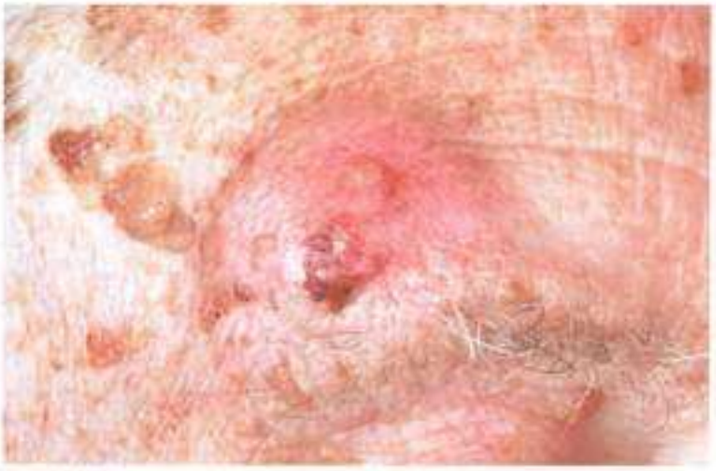


Fig. 11.92 Desmoplastic melanoma. A firm plaque is present, with a small pigmented papule within it, on the forehead and eyebrow.

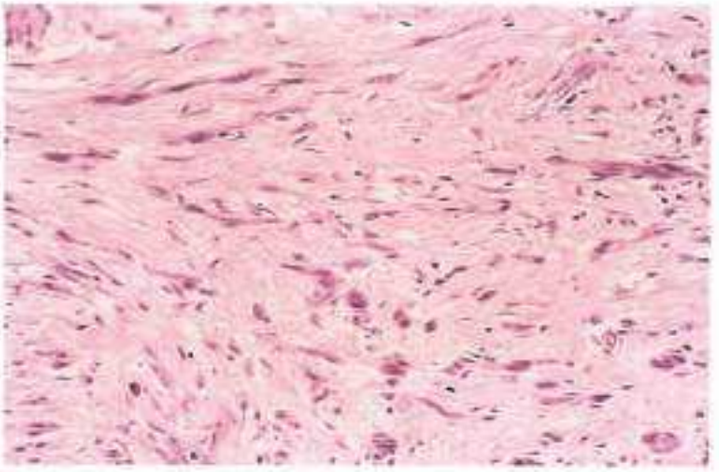


Fig. 11.93 Desmoplastic melanoma. Elongated spindle cells are set in a dense fibrous stroma.

Fontana reaction may reveal small traces of pigment not detected with routine preparations stained with haematoxylin and eosin. S100 markers are usually also positive. Tumours may sometimes show marked pleomorphism with giant cell forms and abundant, often atypical, mitotic figures.

In difficult cases, the finding of mitoses in the dermal component of a melanocytic lesion (excepting juvenile melanoma) is an absolute diagnostic indicator of malignant melanoma. This feature may be valuable in lesions arising from a previously benign melanocytic naevus. Pigmentation is variable but may be heavy, within both malignant melanocytes and melanophages. A lymphocytic infiltrate may be present along the lower border of the lesion and is associated with a better prognosis.

A complete report on a malignant melanoma should include the histogenetic subtype, the level of invasion (Clark's level), the tumour thickness (Breslow thickness), the presence or absence of a lymphocytic infiltrate and an assessment of the mitotic activity of the tumour (mitotic rate recorded as the number of mitotic figures identified per five high-power fields, using a ×300 wide-field objective). High mitotic rate, ulceration, angiolymphatic invasion and microsatellosis are high-risk histological features.

DESMOPLASTIC MELANOMA

Clinical Features

Symptoms

The patient, who is often elderly, may recall a change in a brown patch.

Morphology and distribution

It is often a not particularly pigmented, firm-to-hard plaque or nodule (Fig. 11.92) and commonly occurs on the head or neck.

Histopathology

It is a dermal tumour comprising elongated non-pigmented spindle cells with tapering processes. These are arranged in ill-defined bundles set in a dense connective tissue stroma (Fig. 11.93). They often extend into the subcutaneous fat, and perineural infiltration is often seen.

Differential diagnosis

The most common lesions which enter the differential diagnosis are seborrhoeic warts, pigmented melanocytic naevi, dermatofibromas, angiomas, pigmented basal cell carcinoma, blue naevi, epidermal naevi and trauma. All of these have been dealt with elsewhere, except trauma.

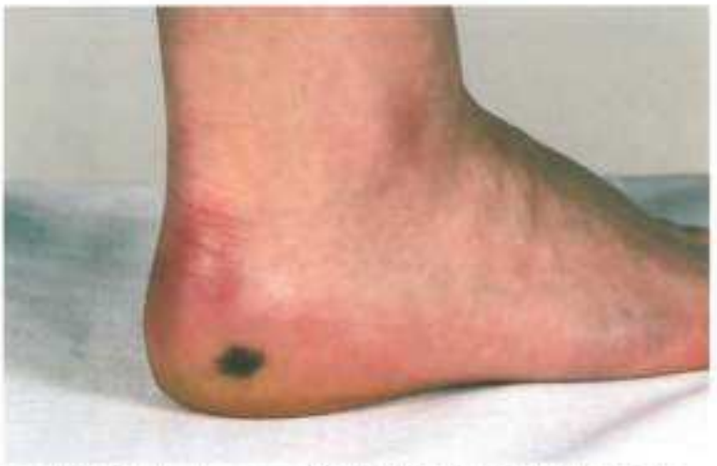


Fig. 11.94 Black heel syndrome. The lesion is usually presented immediately. From a distance the black colour is alarming but the site on the heel, history of vigorous exertion and close examination (Fig. 11.95) shows haemorrhage secondary to trauma.

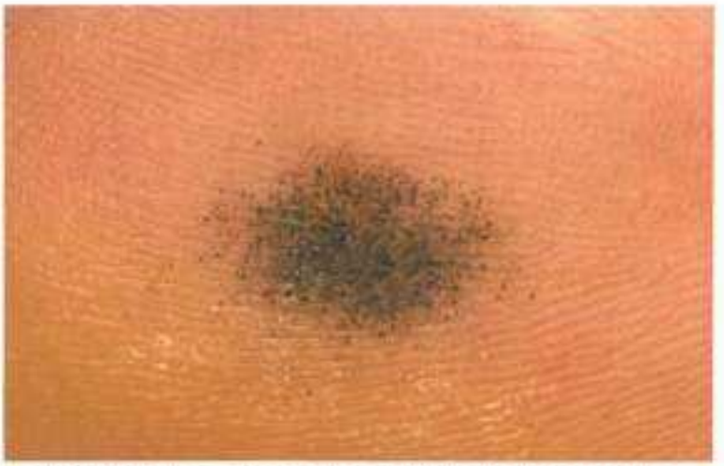


Fig. 11.95 Black heel syndrome. The minute black dots at the edge of the lesion are suggestive of haemorrhage into the skin.

The *black heel syndrome* (Figs 11.94 and 11.95) occurs during vigorous exercise such as playing squash. It is caused by haemorrhage into the stratum corneum secondary to shearing of the papillary capillaries. Paring of the lesion with a scalpel blade reveals flecks of blood in the skin.

Pigmented lesion clinics and 'mole checks' have become standard. It is essential to examine all of the skin. Most patients have their own 'signature' naevi with similar appearing moles to be found elsewhere. Many dermatologists look for and refer to the 'ugly duckling sign' that is a lesion which is not part of the family and is different and if they cannot establish its nature clinically will remove it for pathological examination. Change in colour (particularly darkening), growth in size and change in shape are useful signs. Itch is a poor diagnostic symptom because so many lesions itch (particularly harmless seborrhoeic warts). By the time melanomas bleed, the diagnosis is obvious.

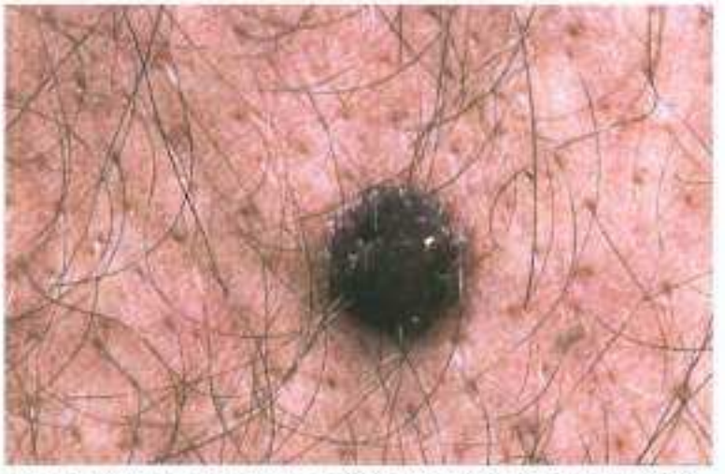


Fig. 11.96 Malignant melanoma. There is a dark brown uniform papule with a black rim, which is characteristic of the vertically invasive melanoma which is frequently misdiagnosed.

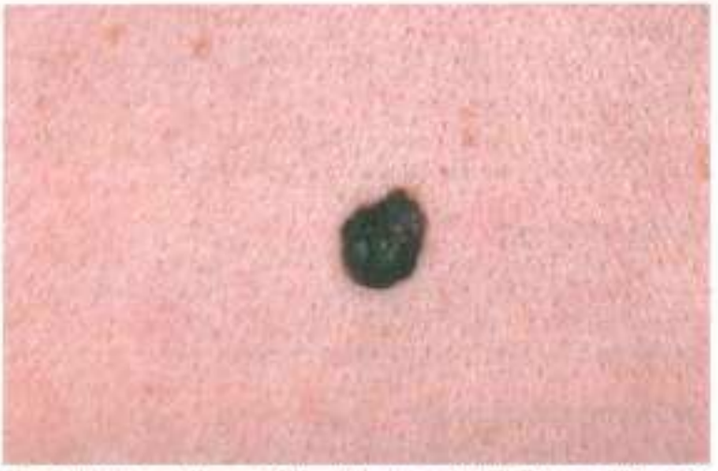


Fig. 11.97 Seborrhoeic wart. Although the lesion is black, it has small pits on its surface, feels rough and looks as if it has been stuck on the skin.

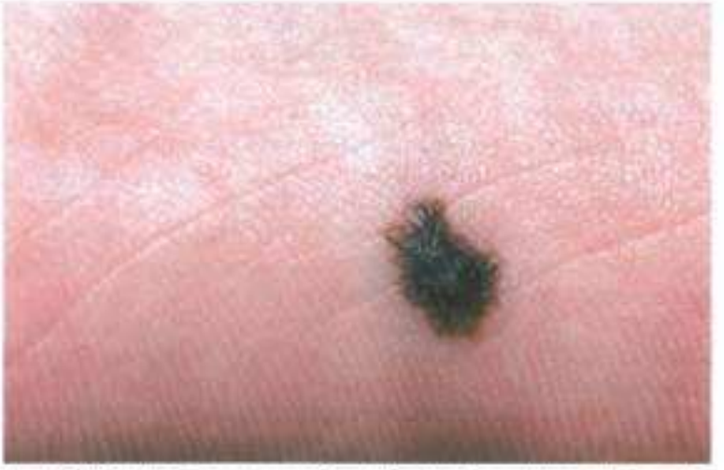


Fig. 11.98 Spindle cell naevus of Reed. This lesion is so dark and because it is not an easy diagnosis to be sure of clinically it should be excised for histology although it is quite benign.

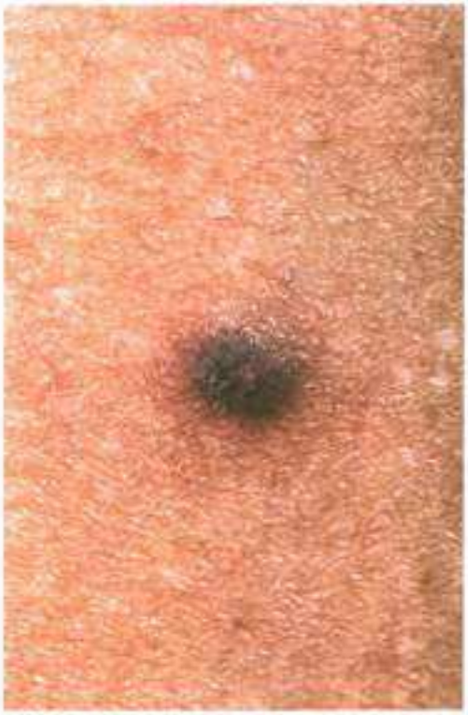


Fig. 11.99 Dermatofibroma. The lesion is pigmented but it feels different from a melanoma. It is firm and may be gripped between the index finger and thumb and moved within the dermis.

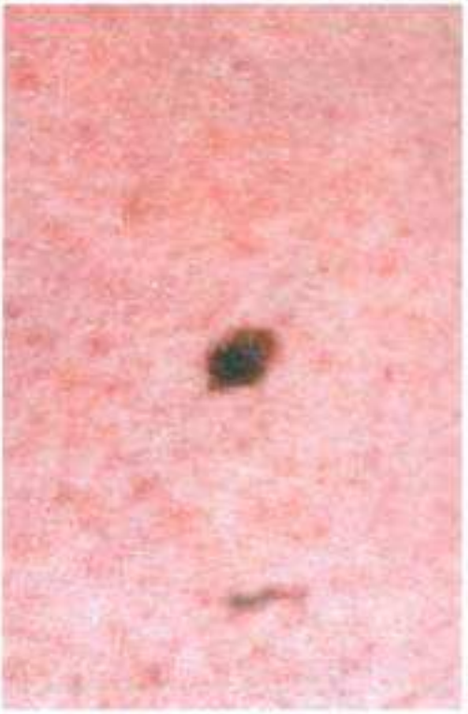


Fig. 11.100 Dysplastic naevus. There are only two shades of brown quite evenly distributed which is reassuring, but dysplastic naevi occasionally change their nature and should therefore be excised.

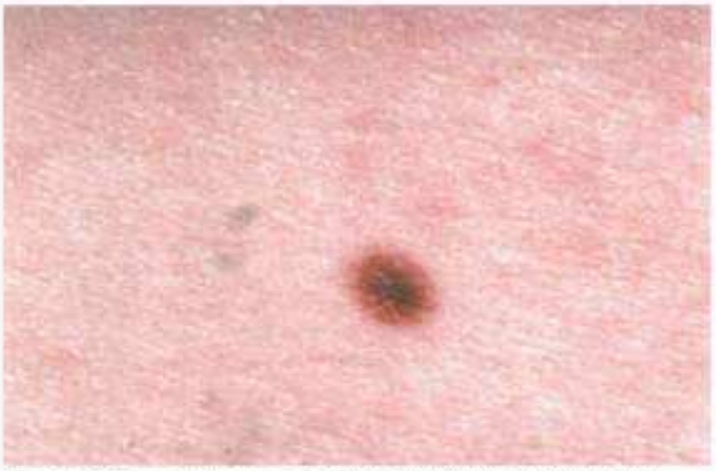


Fig. 11.101 Compound naevus. This is an entirely benign mole with brown centre and light brown surround and the patient can be reassured.

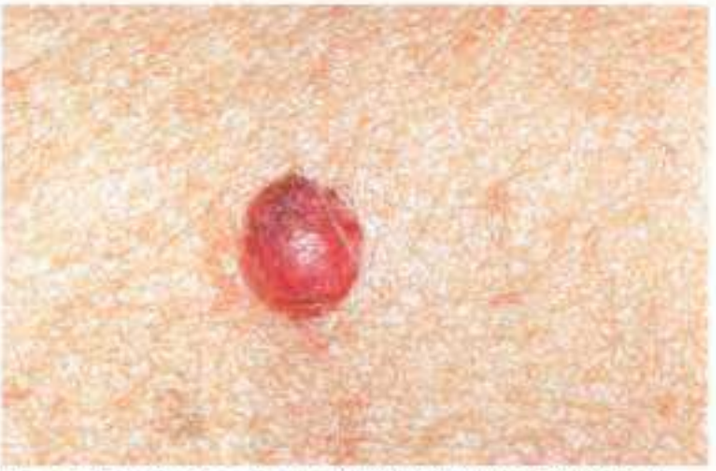


Fig. 11.102 Amelanotic melanoma. Although the majority of the mole is an even red-brown, the top of it is irregularly pigmented, which should alert the physician to its malignant nature. It was 2.3 mm Breslow thickness.

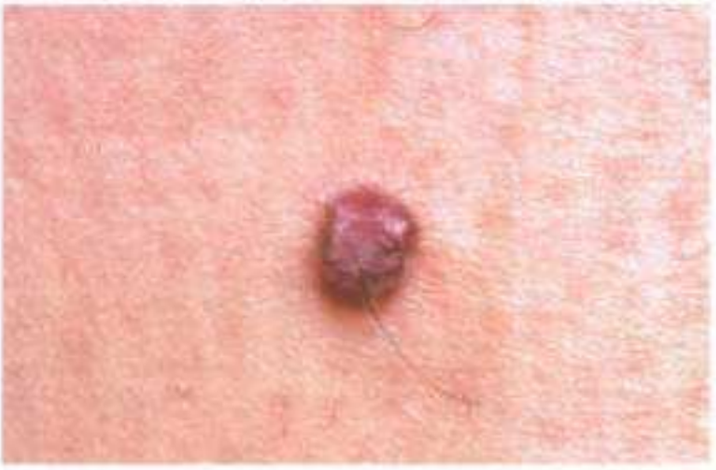


Fig. 11.103 Haemangioma. The colour is the distinguishing feature. It is red or purple and dermatoscopic examination will illuminate and magnify the colour further if there is any doubt.

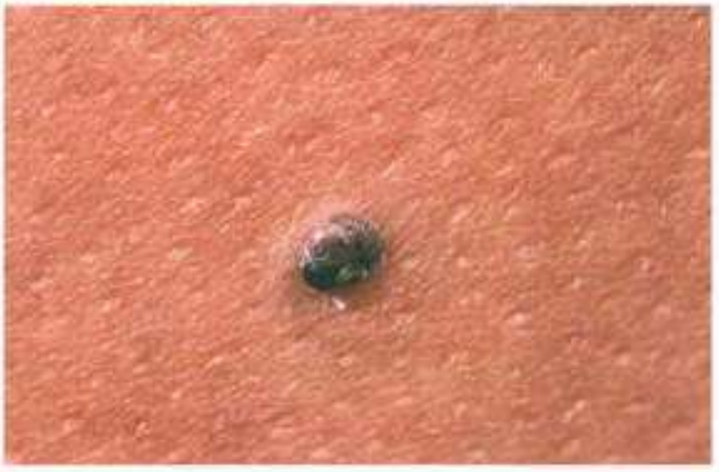


Fig. 11.104 Angiokeratoma. The lesion is dark but the colour is purple (and the dermatoscope is useful here) with a keratinous, warty surface.

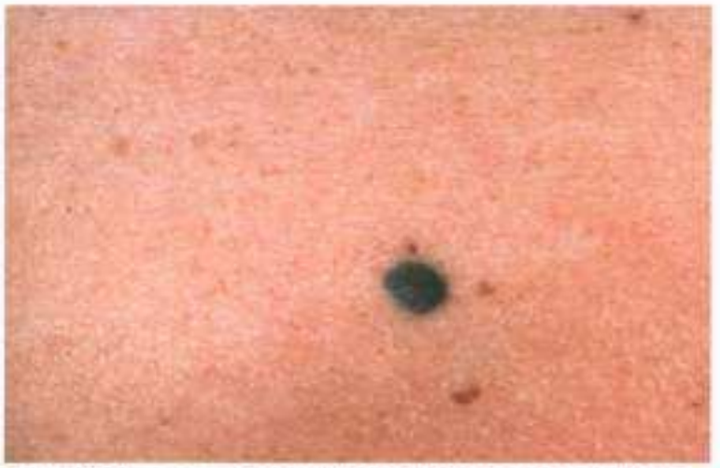


Fig. 11.105 Blue naevus. Once more the colour is so important in making the distinction from a melanoma. This benign mole is blue or blue-black.

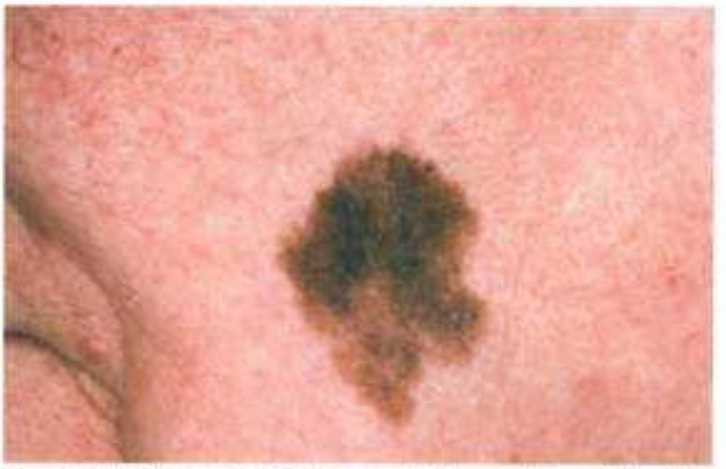


Fig. 11.106 Lentigo maligna. There are a variety of areas of pigmentation with a sharply indented and scalloped margin on the cheek (a classic site) in a sun-damaged elderly person, although younger patients are now at risk (she was only 62).

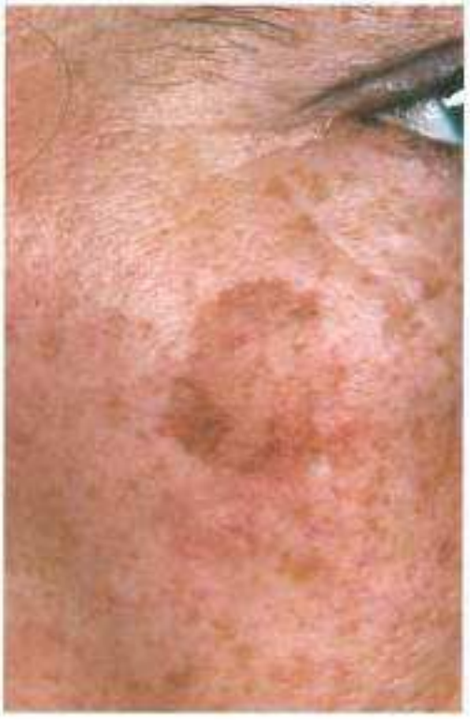


Fig. 11.107 Solar lentigo. The lesion is a liver colour and often has a matt surface and does not have the deep pigmentation or uneven margin of a malignant lentigo. Note the surrounding smaller lentigines.

The A (Asymmetry) B (Border irregularity) C (Colour variability) D (Diameter greater than 6 mm) mnemonic is helpful for melanomas which have a horizontal growth phase but does not pick up rapidly growing invasive melanomas so E for Evolution has been added. The common lesions that enter into the differential diagnosis of papular melanomas (Figs 11.96–11.105), lentigo maligna (Figs 11.106 and 11.107) and superficial spreading melanomas (Figs 11.108–11.111) are illustrated.

Management of malignant melanoma

Surgery

Surgery is, at present, the only definitive treatment for malignant melanoma. In the horizontal radial growth phase, the lesion can usually be excised and primarily repaired. If vertical invasion has occurred, then surgical intervention has traditionally been more aggressive with wide excision and grafting (Fig. 11.112). This, however, is quite arbitrary and, despite at least three large randomized trials, there are no statistically significant data that favour wide over narrow margin excision. It is, however, probably a reasonable policy to excise a melanoma with a 1 cm clearance for every millimetre of invasion, although many would doubt whether greater than 2 cm is necessary, however deep the lesion is.

Site constraints influence the margin of excision. Lentigo maligna, despite the fact that it is so visible and ought to be diagnosed early, is often quite sizeable at presentation; consequently, definitive surgery may be disfiguring. In principle, the lesion should be excised and the defect repaired, but some dermatologists prefer to observe large lesions and intervene only if it becomes thickened and biopsy confirms the development of a lentigo maligna melanoma, since the malignant potential is low and the patient is often elderly and infirm. Serial photographs of the lesion may be helpful in deciding when to operate. Radiotherapy, cryotherapy and topical imiquimod have their advocates in this early stage.

Sentinel node biopsy

If the lymph nodes are clinically involved, they should be removed, but there is controversy as to whether they should be removed prophylactically if they are clinically uninvolved. The number of nodes involved is an important factor determining prognosis and overall survival. Sentinel node mapping is a technique for detecting occult micrometastases in the lymph nodes. Positive results are proportional to the Breslow thickness of the tumour. Therefore, in melanomas less than 1 mm in depth, micrometastases are unlikely. Approximately 18% of patients with tumours 1–3 mm thick and half of 3–4 mm thick do have micrometastases. Elective lymph node dissection has not yet been proven to be life saving, particularly because adjuvant therapy of melanoma is still not very successful despite high-dose adjuvant interferon alfa-2β. However there is a vogue for pre-operative lymphoscintigraphy to identify the drainage from the tumour.

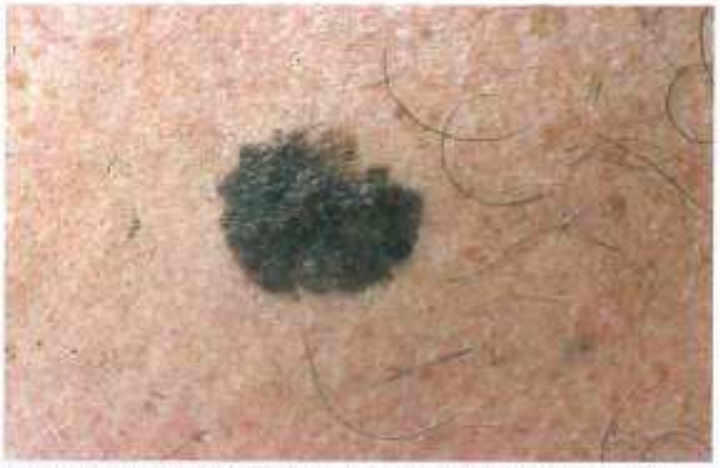


Fig. 11.108 Superficial malignant melanoma. The scalloped irregular well-defined margin with a multiplicity of shades of melanin pigmentation is characteristic.

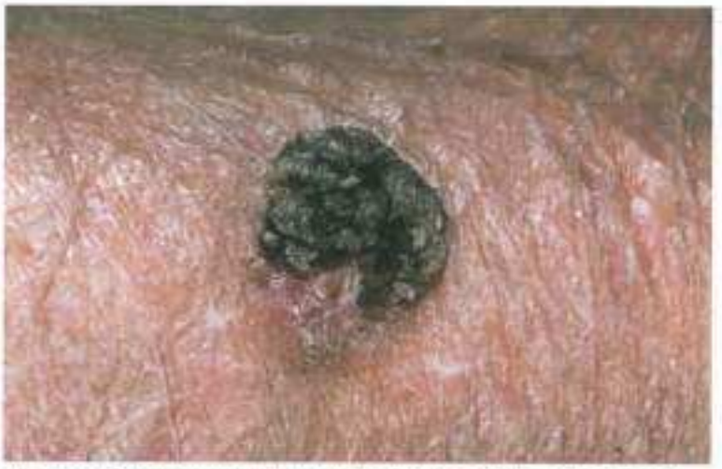


Fig. 11.109 Seborrhoeic wart. The surface is warty and fissured and almost appears to be 'stuck on' the skin. It is harmless but is probably the most common lesion requiring a diagnostic opinion.

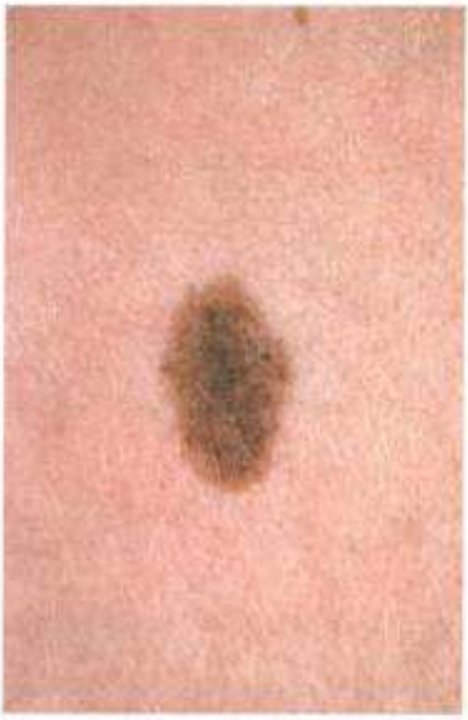


Fig. 11.110 Congenital melanocytic naevus. These larger birth marks occasionaly do evolve into a superficial malignant melanoma. The arrangement of the pigment here is very regular and is benign, but such lesions should always be protected from the sun.

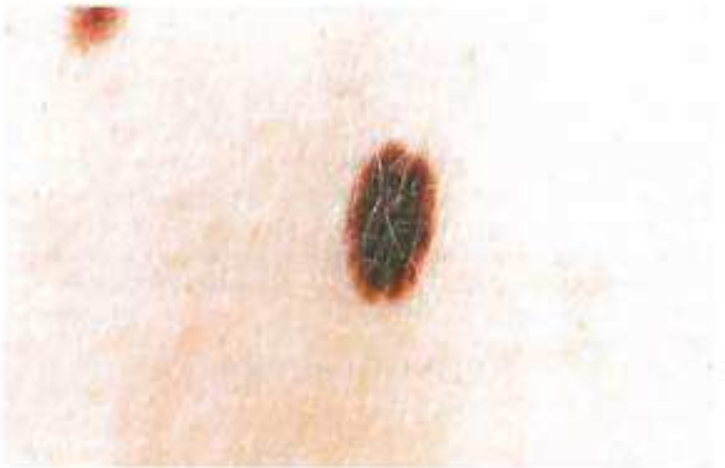


Fig. 11.111 Compound melanocytic naevus. The majority of the lesion is dark brown but it does have a light round surround. It is perfectly regular and benign.

which may be ambiguous in sites such as the mid trunk, head and neck, shoulder and proximal upper extremity. This is combined with intraoperative lymphatic mapping using a blue dye to identify the first node in the lymphatic drainage. This node is selectively dissected out for histological examination and, if positive, a block dissection follows. The technique may well be important for patients who have a tumour of Breslow thickness greater than 3 mm, but clinical trials are necessary to establish whether patients with lesions less than 1 mm or even 2 mm should be offered this

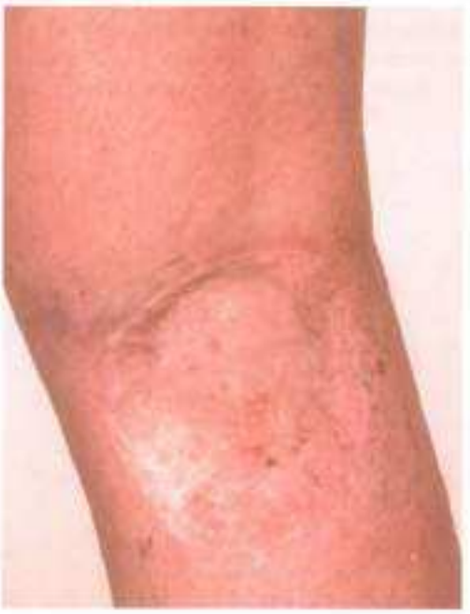


Fig. 11.112 Skin grafting. The traditional aggressive therapy even for thin melanoma was wide excision and grafting. It is now mainly reserved for deeper lesions and where site constraints do not allow adequate excision.

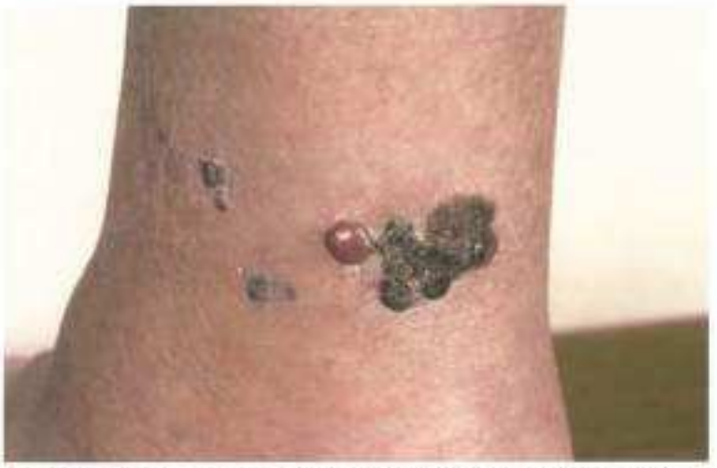


Fig. 11.113 Metastatic malignant melanoma. Local spread from this invading superficial malignant melanoma has produced a plum-coloured nodule as well as pigmented papules.

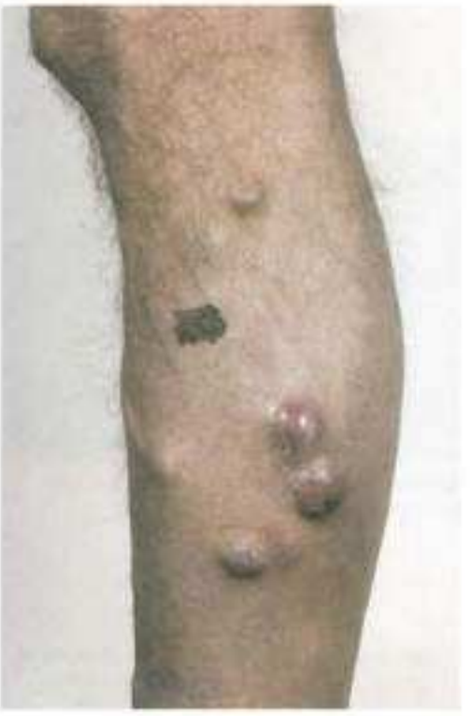


Fig. 11.114 Metastatic malignant melanoma. Firm flesh and plum-coloured tumours have evolved from this man's neglected and now regressed malignant melanoma.

technique. There is an attendant morbidity and unfortunately 20% of patients who are SLN negative experience recurrences and there may be false positivity. Ultrasonography has its advocates. A D2-40 antibody which reacts with endothelial cells of the lymphatics may become a useful immunohistochemical marker for tumour cells within the lymphatics.

Radiotherapy

There is a place for radiotherapy in lentigo maligna.

Chemotherapy

Most dermatologists work with an oncologist specializing in metastatic melanoma. A number of drug regimens have been used to treat metastatic disease (Figs 11.113–11.114), including interferon, vindesine, vinblastine and dacarbazine. Perfusion of isolated limbs with cytotoxic drugs including melphalan has been used for axillary or inguinal lymph node involvement. Vaccines are under investigation. Lasers may be used for local cutaneous metastases.

Approximately half of melanomas have an activating mutation in the gene encoding the serine-threonine protein kinase BRAF (also found in papillary and anaplastic thyroid cancers). 90% of these have a substitution of glutamic acid for valine at amino acid 600 (the V600E mutation). Significant remissions are being obtained with Vemurafenib, a $BRAF^{V600E}$ inhibitor. Resistance however, occurs after approximately one year, as other members of the NRAS-RAF-MEK-ERK pathway are upregulated and the cancer is not dependent on BRAF anymore. However, other BRAF inhibitors (viz. Dabrafenib) are combined targeted gene therapy with MEK inhibitors and Ipilimumab, a human monoclonal antibody which blocks the CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) inhibitory signal in melanoma and permits cytotoxic T lymphocytes to destroy malignant cells, hold promise for the future.

Topical imiquimod

5% imiquimod applied for 5 days a week for 12 weeks produces an inflammatory response and seemingly good results in lentigo maligna.

Prevention

The most important goal is prevention by widespread education regarding the dangers of ultraviolet light and sunburn, the use of sunscreens and other means of photoprotection, and the features of malignancy. This will allow the diagnosis to be made early by patients and doctors alike.

Mycosis fungoides and lymphoproliferative disorders of the skin

12

The study of cutaneous lymphomas has been greatly advanced by immunopathological and molecular techniques including gene rearrangement studies on paraffin-embedded (as opposed to fresh) tissue. CTCLs (cutaneous T cell lymphomas) have been classified by the WHO and EORTC (European organization for research and treatment of cancer) into two broad categories of mycosis fungoides and Sézary syndrome and non-mycosis fungoides CTCLs which are much less common and classified by clinical behaviour, pathology and immunodiagnosis.

Mycosis fungoides is the commonest. It has various precursor states that may or may not progress to frank cutaneous lymphoma (*parapsoriasis*, (Fig. 12.1), *Woringer–Kolopp disease*, *poikiloderma atrophicans et vasculare* and *follicular mucinosis*). In its fully expressed form, mycosis fungoides is a malignant proliferation of helper $CD4^+$ T lymphocytes which disseminate throughout the lymphoreticular system, although for the majority of patients it represents a benign reactive process that never spreads. The *Sézary syndrome* is an erythroderma with so many features in common with mycosis fungoides that it is believed to be an aggressive leukaemic overspill.

The other non-mycosis fungoides T cell lymphomas embrace:

- $CD30^+$ diseases including the benign condition *lymphomatoid papulosis* and the malignant *anaplastic large cell lymphoma* (ALCL) with its attendant t(2;5)(p23;q35) translocations. Intermediate forms do exist.
- $CD8^+$ lymphomas – usually a subcutaneous panniculitic α/β TCR (T cell receptor) type.
- NK/T nasal type which is $CD56^+$ associated with the Epstein–Barr virus.
- Aggressive epidermotropic $CD8^+$ Burkitt's type lymphoma affecting the skin.
- Gamma/delta $CD3^+$ lymphoma.
- $HTLV\text{-}1^+$ AITCL.

B cell disorders such as *non-Hodgkin's lymphoma* may affect the skin, but usually the disease is already established in the lymph nodes. Occasionally, it may present and remain in the skin for a limited period before becoming systemic. Primary cutaneous B cell lymphomas do, however, occur.

Cutaneous B cell lymphomas may be classified into

- *Indolent* with greater than 95% 5-year survival and include
  - Primary cutaneous marginal zone B cell lymphoma which is $Bcl\text{-}2^+$ 6^-
  - Follicle centre which is $Bcl\text{-}2^-$ 6^+
- *Aggressive*
  - Diffuse large B cell lymphoma leg type
  - Diffuse large B cell lymphoma (other).

Hodgkin's disease rarely involves the skin although pruritus, ichthyosis and cutaneous infections secondary to immunosuppression may occur.

Secondary deposits from multiple myeloma and myeloid leukaemia may occur in the skin. Occasionally, an identical skin eruption to mycosis fungoides may occur in association with Hodgkin's disease or adult T cell lymphoma/leukaemia.

Finally, *Jessner's lymphocytic infiltrate* and a pseudolymphoma of the skin (*lymphocytoma cutis*) are described since they may simulate the clinical appearance of lymphoma and have a dense lymphocytic infiltrate, but they are benign.

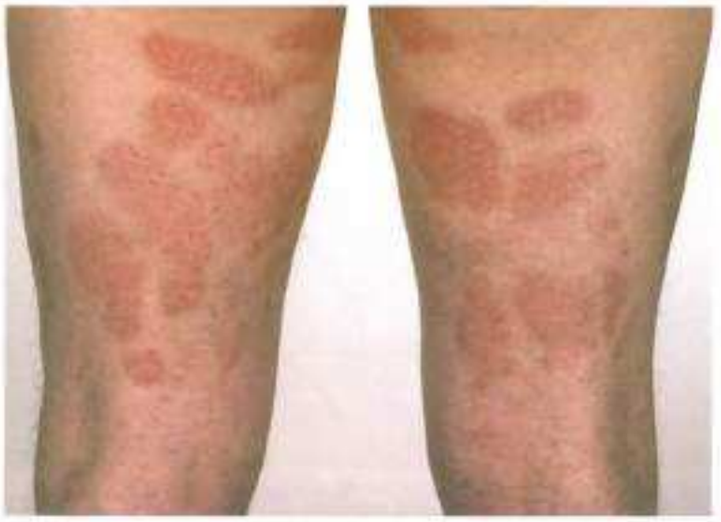


Fig. 12.1 Parapsoriasis. The term was originally introduced to embrace a collection of disorders that were like psoriasis in that they were chronic, inflammatory, asymptomatic, untreatable and of unknown aetiology.

Small, benign type parapsoriasis en plaques

A persistent, benign, symmetrical uniform eruption of the trunk and limbs, often with a finger-like or digitate pattern, which may represent an abortive cutaneous T cell lymphoma.

Aetiology

Small plaque parapsoriasis is uncommon, occurs in all races, is more frequent in males and begins in middle age. The cause is unknown. Its appearance is distinctive and it can be separated from the premycotic large plaque type of parapsoriasis; however, occasionally, the histology is that of mycosis fungoides and a dominant T cell clone may be demonstrated.

Clinical Features

Symptoms

The lesions are disfiguring but asymptomatic.

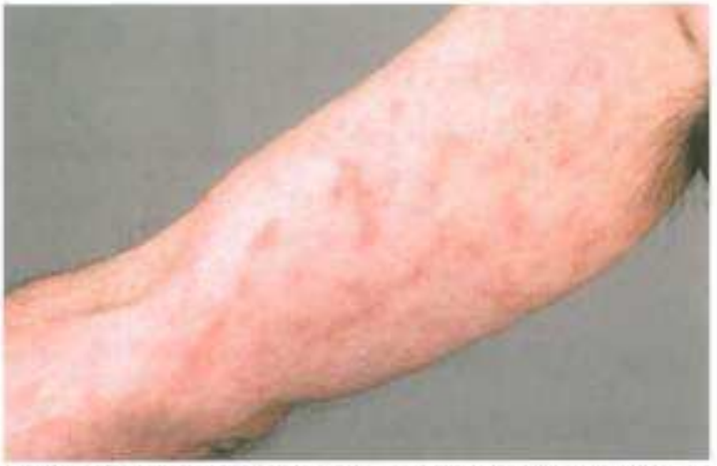


Fig 12.2 Digitate dermatosis. The lesions are pink, fairly round or oval, flat and atrophic.

Morphology

The lesions are fairly round, or oval, well defined and flat (Fig. 12.2). Their colour is pink, red, brown or even slightly yellow, and, therefore, the condition was formerly called *xanthoerythroderma perstans*. Overall, the morphology is uniform and the patches are less than 5 cm in diameter, although they may be slightly larger on the proximal aspects of the limbs. A fine scale with a wrinkled, atrophic or 'cigarette paper' appearance is often discernible. A very characteristic variant (often known as *digitate dermatosis*) consists of finger-like processes (Figs 12.3 and 12.4), which may follow dermatomes or lines of cleavage of the skin.

Distribution

The lesions are most noticeable on the sides of the torso, the backs of the thighs and inner aspects of the arms and legs and are symmetrical.

Management

A skin biopsy is essential because parapsoriasis may simulate the premycotic stage of mycosis fungoides known as large patch parapsoriasis, which is asymmetrical, has larger patches and plaques, varied colours and irregular well-defined outlines. Poikiloderma may also be present which does not occur in small benign type parapsoriasis. The prognosis is excellent, but follow-up biopsies may be necessary if there is any suspicion of progression. Treatment is usually required because of the unsightly appearance. Although not curable, it is responsive to narrowband ultraviolet light or photochemotherapy.

Mycosis fungoides

The commonest cutaneous T cell lymphoma, which usually has a benign course but may evolve into a malignant proliferation of $CD4^+$ T lymphocytes and invade the skin, lymph nodes and virtually all internal tissues.

Aetiology

The aetiology is unknown. First described by Alibert in 1806, and renamed mycosis fungoides because of the mushroom-like tumours that arise in the later stages of the disease, it is a rare condition that can present at any age, including childhood, and occurs in all races (Figs 12.5 and 12.6) and both sexes. There is occasionally clustering of the disease in families and there have been reports of first-degree relatives having more haematopoietic or lymphoproliferative malignancies than would be expected, but essentially genetic studies are unrevealing.

Mycosis fungoides is a helper T cell malignancy that commences in the skin. Using the polymerase chain reaction to amplify rearrangements of the T cell receptor, it has been shown that there are clonal cells in early mycosis fungoides but these are much more pronounced in later stages of the disease and in lymph node involvement. It would appear, therefore, that it is a neoplasm of skin-associated lymphoid tissue (SALT) and that cells travel between the skin and lymph nodes via the blood and lymph. The finding of T cell gene rearrangements in the early stages of the disease, although biologically interesting, is at the moment not clinically relevant to staging the disease because mycosis fungoides is a disorder with a highly variable outcome, ranging from an indolent disease lasting a lifetime without harming the patient to a disorder with an aggressive course and dismal prognosis. What event or cofactor selects out the malignant clone

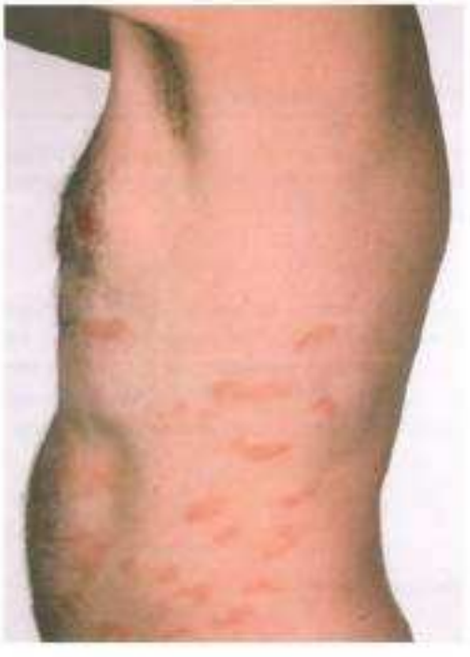


Fig. 12.3 Digitate dermatosis. This condition is also known as parapsoriasis en plaque (small and benign type), or chronic superficial scaly dermatosis of Calnan and Mears.

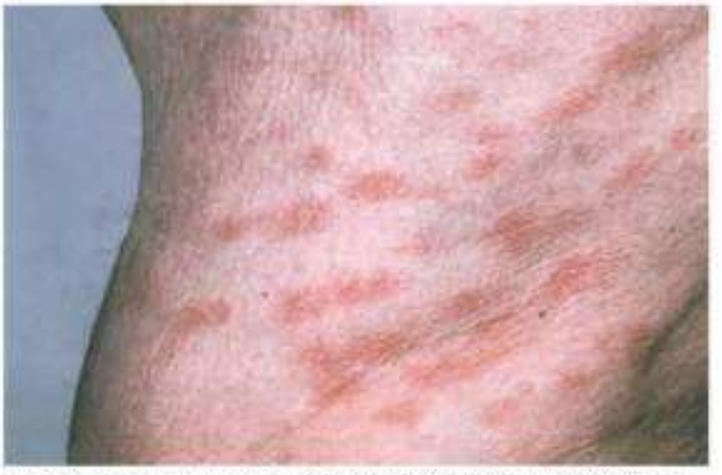


Fig. 12.4 Digitate dermatosis. Uniform linear finger-like processes occur. The histology is fairly non-specific, only occasionally showing abnormal T cells and epidermotropism. It may be regarded as an abortive variant of mycosis fungoides.

Fig. 12.5 Mycosis fungoides. The lesions exhibit various shades of pigment in a black skin but the asymmetrical and sharply angulated shapes are very characteristic. The patient was dead within 4 years of developing the disorder.

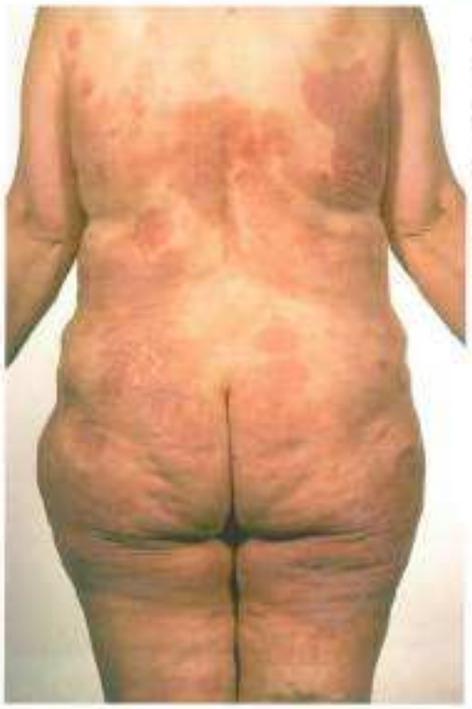


Fig. 12.6 Mycosis fungoides. In a white skin, the lesions show various shades of pink and red but the shapes are similar to those in Figure 12.5. She began to develop the disease at the age of 9 but remained well until she died 70 years later of an unrelated disease.

during the course of mycosis fungoides and permits it to progress and metastasize is not known. There has been considerable interest in retroviruses because of similarities between the skin lesions of adult T cell lymphomas/leukaemia, which is known to be related to human T cell leukaemia/lymphoma virus type 1 (HTLV-1), and those of mycosis fungoides and the Sézary syndrome.

Clinical Features

Symptoms

In the early stages, although unsightly, it is asymptomatic but may be sore in winter. Itching is a feature of progression.

Morphology

Bazin in 1870 suggested that mycosis fungoides was a disorder that progressed from a premycotic stage to discrete plaques and tumours. The premycotic *patch stage* begins as barely palpable patches on the trunk and limbs. The patches are pink or red and may easily be mistaken for eczema or psoriasis and delay in diagnosis for many years is not uncommon (Figs 12.7 and 12.8). However, the lesions do not respond to the standard treatment for these diseases and this in itself may suggest the diagnosis. The lesions are much larger than the small benign type and average 10–20 cm in diameter and commence much earlier. They become widespread on the trunk and limbs and favour the breasts and buttocks. The patches tend

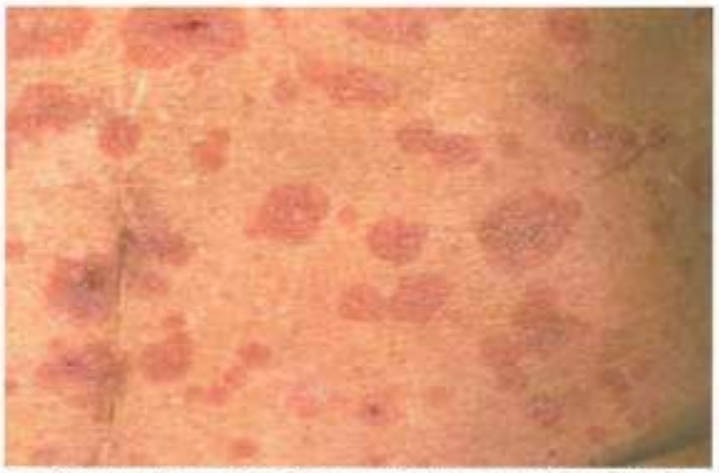


Fig. 12.7 Mycosis fungoides. The premycotic stage may easily be mistaken for psoriasis or eczema, but the atrophy, wrinkling, and angulated, well-defined shapes of the lesions may suggest the need for a biopsy.

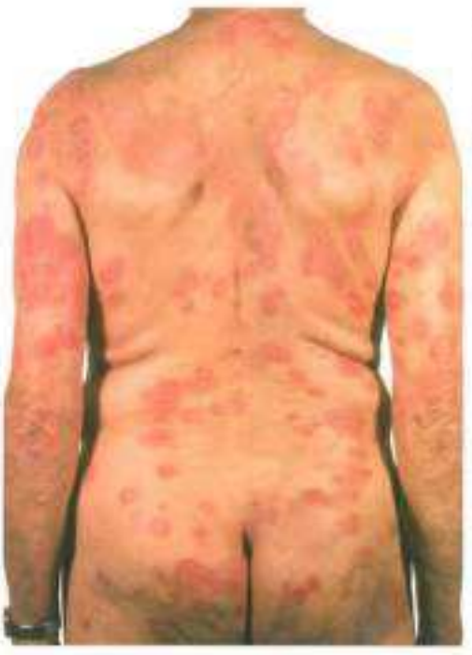


Fig. 12.8 Mycosis fungoides. Widespread lesions simulating psoriasis are present. However, they are asymmetrical, which is unusual for psoriasis. TH17 positivity is characteristic of the psoriatic type of mycosis fungoides. (Courtesy of Dr A. C. Pemberton.)

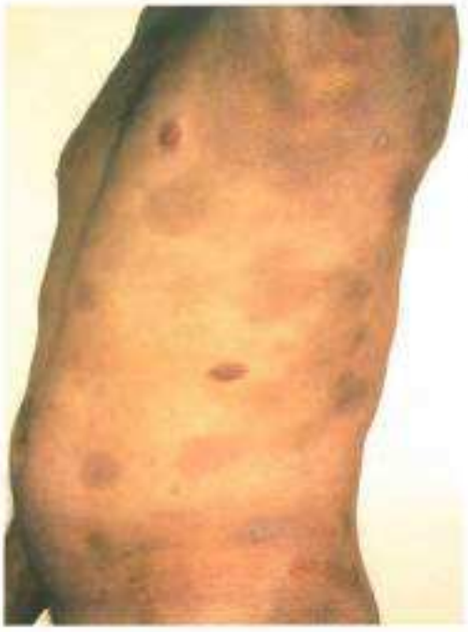


Fig. 12.9 Mycosis fungoides.
The patches vary in colour depending on the depth of the infiltrate. There is considerable postinflammatory hyperpigmentation in many of the lesions.

to be asymmetrical and vary in colour (Fig. 12.9), being pink and various shades of red (Fig. 12.10). The lesions may be quite angulated and bizarre in shape and are often annular (Fig. 12.11), rather than just round or oval. In addition, their surface may be scaly and finely wrinkled, with cigarette paper-like atrophy. In pigmented skin, the lesions may be hyper- or hypopigmented (Fig. 12.12), with some scaling and atrophy, which may suggest the diagnosis. Poikiloderma is often present (Fig. 12.13). This term refers to a striking appearance of telangiectasia, atrophy and a combination of hyper- and hypopigmentation of the skin. One or a limited number of patches may occur, particularly over the breasts or buttocks, or the whole eruption is made up of these poikilodermatous patches (Fig. 12.14) and the condition is known as *poikiloderma atrophicans et vasculare*.

As the condition progresses, the lesions become more infiltrated (Fig. 12.15). This *plaque stage* is relatively easy to diagnose. The lesions are palpable and thickened, and deeper in colour. They often become intolerably pruritic. Ultimately, the tumorous stage develops. The lesions are of a red-brown or purple colour and consist of nodules (Fig. 12.16), which may be mushroom-like (Fig. 12.17) or ulcerated (Fig. 12.18). The lesions become extensive (Fig. 12.19).

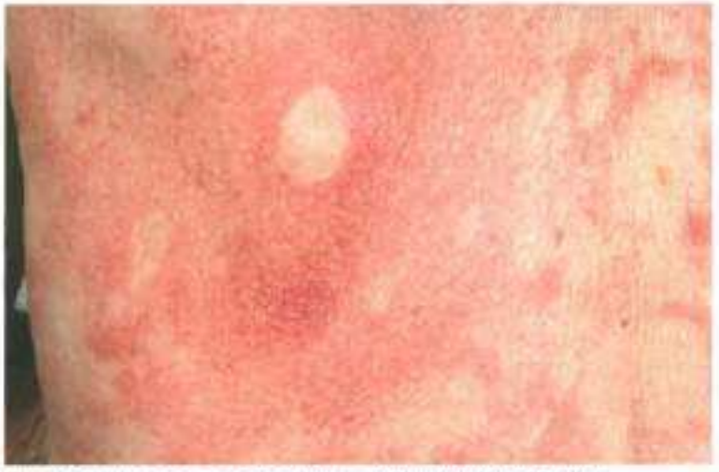


Fig. 12.10 Mycosis fungoides. There are different shades of red and poikiloderma. Occasionally islands of spared normal skin are present, a characteristic it shares with pityriasis rubra pilaris.

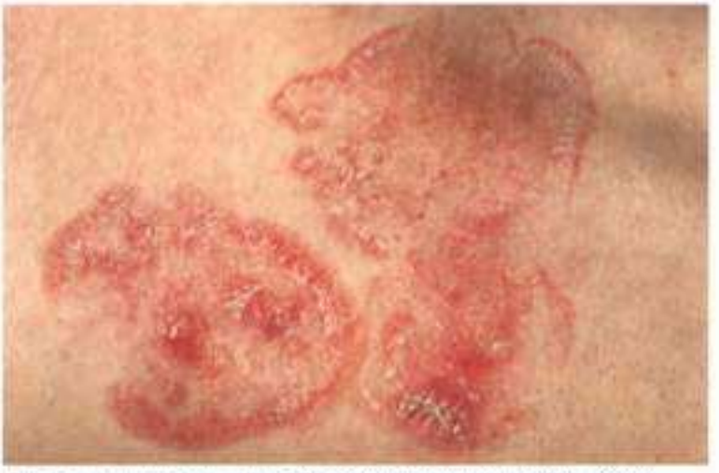


Fig. 12.11 Mycosis fungoides. The red scaly plaque on the left is arciform (an incomplete circle) and on the right is polycyclic. This is typical in mycosis fungoides.

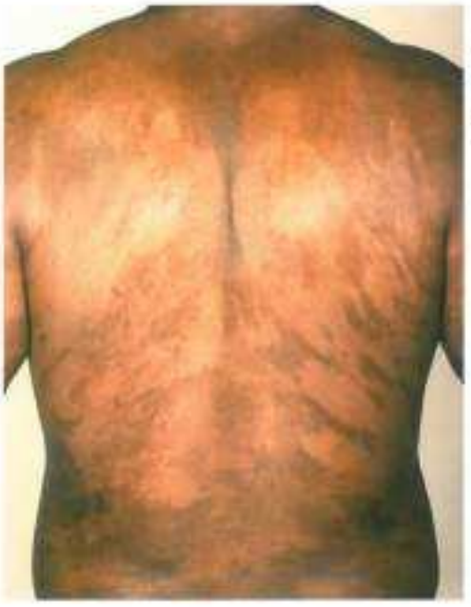


Fig 12.12
Hypopigmented mycosis fungoides. In dark skin, the lesions may be hyper- or hypopigmented.

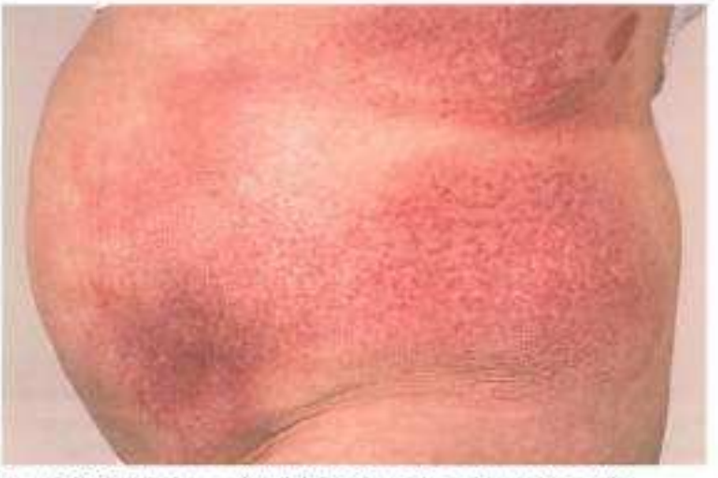


Fig. 12.13 Poikiloderma. A well-defined large plaque is present over the buttock, a common site. There is pronounced telangiectasia.

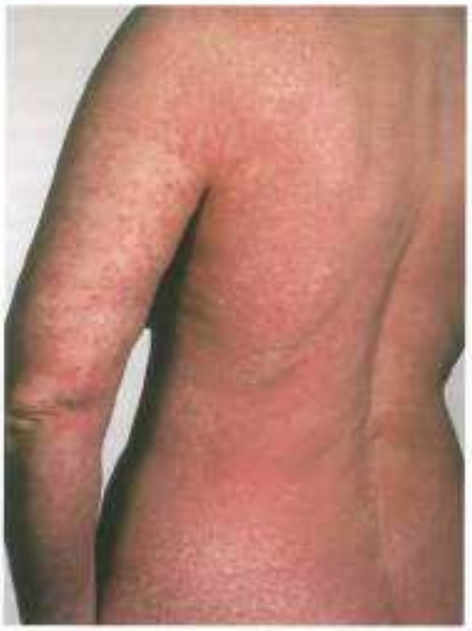


Fig. 12.14 Poikiloderma atrophicans vasculare. Very occasionally the whole eruption has the features of poikiloderma. The prognosis is good. The disease began in this patient when she was 16 years of age. She is now 75. She has been free of visible disease for 30 years with low-dose psoralen plus ultraviolet A.

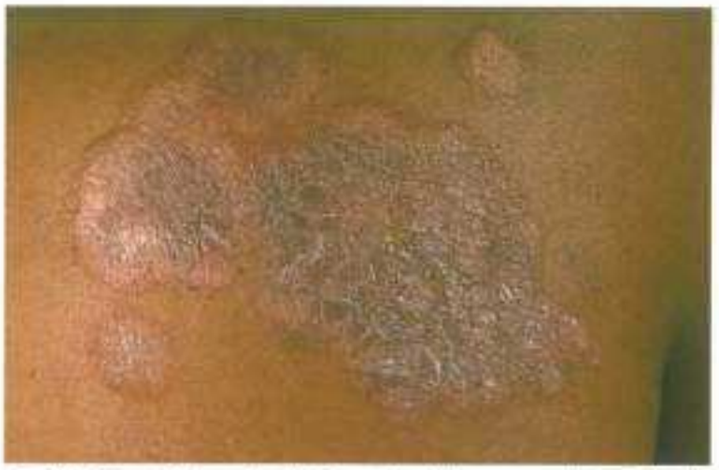


Fig. 12.15 Mycosis fungoides. Lesions gradually become more infiltrated as the disease progresses. These plaques were annular in shape. The redness is visible in dark skins although hyperpigmentation is often prominent. The buttocks are invariably involved.

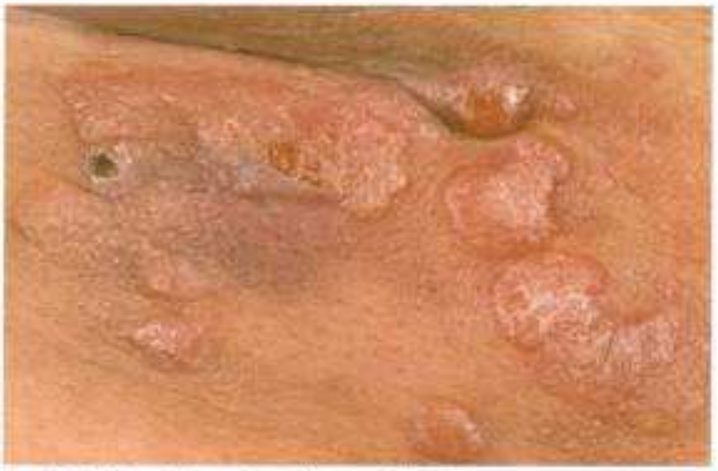


Fig. 12.16 Mycosis fungoides. All stages of the disease are present, with patches, plaques and tumours, some showing incipient ulceration. Tumours develop in 8% and are an ominous sign.

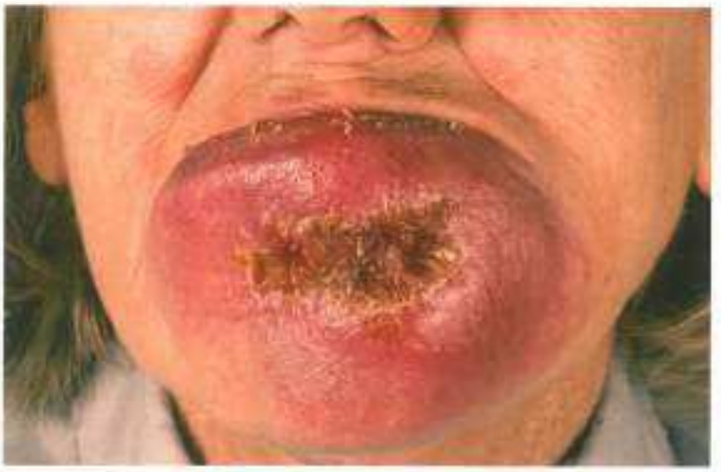


Fig. 12.17 Tumour-stage mycosis fungoides. The nodules are purple in colour. This mushroom-like appearance gave rise to the name mycosis fungoides.

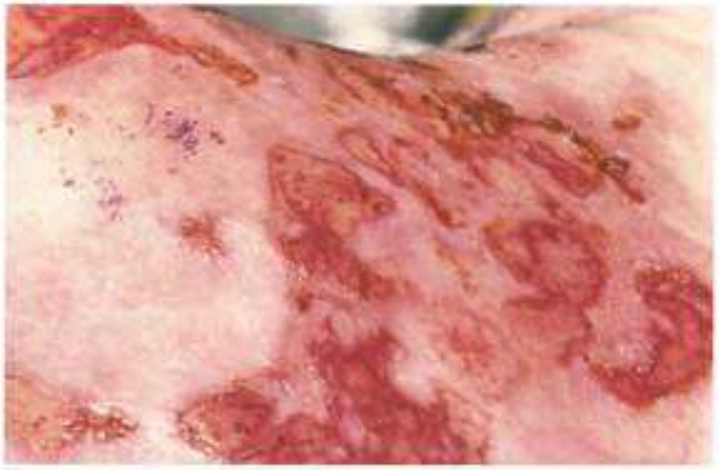


Fig. 12.18 Ulcerative mycosis fungoides. Very occasionally ulcerative lesions occur. They responded to psoralen plus ultraviolet A but ultimately the patient succumbed.

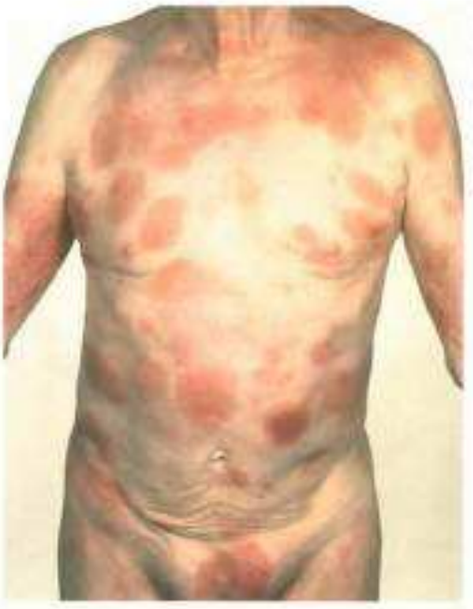


Fig. 12.19 Mycosis fungoides. As more lymphocytes are attracted to the skin, the lesions become a deeper shade of red. Note the asymmetry and the variations of colour.

Very occasionally, isolated plaques of mycosis fungoides may occur. This is known as *Woringer–Kolopp disease* (or *Pagetoid reticulosis* because the abnormal cells are confined to the epidermis with numerous mitoses at the dermo-epidermal junction). There is a single verrucous plaque, usually on the extremities (Fig. 12.20), with polycyclic borders and central clearing. It may represent significant host resistance to the disease. It appears to arise from a proliferation of an abnormal clone in the epidermis. Mycosis fungoides can occur as a single lesion (unilesional mycosis fungoides) but it appears more like a patch or plaque of mycosis fungoides and the invasion of the dermis by atypical mononuclear cells is the same as that of mycosis fungoides.

The progress from minimally infiltrative plaques to the *tumour stage* may take a lifetime, or a few years, or never occur at all. The development of tumours is an ominous sign and the lymph nodes, liver, spleen and other organs are likely to be involved. Patients then succumb to the consequences of destruction of the internal viscera, vascular obstruction or overwhelming infection.

Histopathology

Mycosis fungoides is a malignant tumour of $CD3^+$, $CD4^+$ (rarely $CD8^+$ instead) and $Ro45^+$ T lymphocytes, i.e. those with the phenotype of helper T cells (Fig. 12.21). In early patch stage disease, they are recognized as medium-sized (<12 μm) cells with an irregular hyperchromatic nucleus (Lutzner cells). In later stages, much larger cells (15–30 μm) with highly convoluted (cerebriform), hyperchromatic nuclei become apparent, known as mycosis/Sézary cells. These cells are present in the peripheral blood in Sézary syndrome (Fig. 12.22), and occasionally may be detected to a much lesser extent in mycosis fungoides and other benign dermatoses. Electron microscopically they are characterized by multilobed, convoluted nuclei with peripheral chromatin margination (Fig. 12.23).

In the patch stage, there is infiltration of the epidermis and dermis by mycosis cells (Fig. 12.24). In plaque stage mycosis fungoides, the epidermis is often acanthotic and psoriasiform. The infiltrate is much more intense and has an affinity for the epidermis (epidermotropism) and may form intraepidermal collections known as Pautrier microabscesses. Some of the cells are large with hyperchromatic, convoluted, irregular and cerebriform nuclei (mycosis fungoides cells). Adnexal epithelium, particularly hair follicle, may be involved. The dermis, which is sometimes fibrosed, contains a dense, sometimes lichenoid, infiltrate, which may contain eosinophils and histiocytes in addition to lymphoid cells.

In tumorous mycosis fungoides, dense infiltrates occupy both the dermis and the subcutaneous fat. Typically, pleomorphism is much more marked

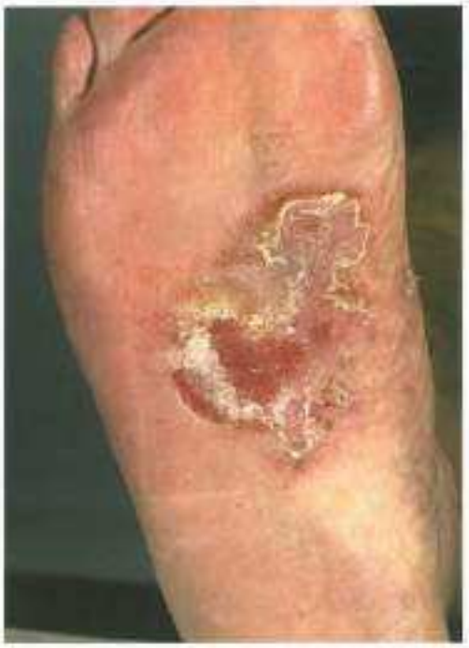


Fig. 12.20 Woringer–Kolopp disease. A solitary patch of mycosis fungoides (also known as Pagetoid reticulosis) may occur. The abnormal cells are confined to the epidermis and it may represent significant host resistance to the disease.

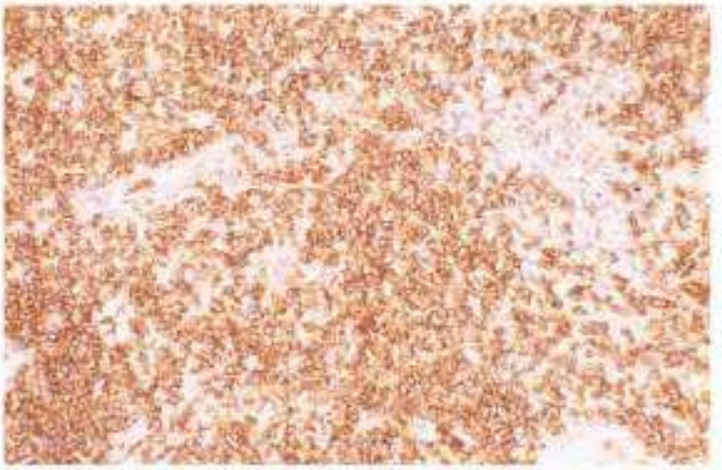


Fig. 12.21 Tumour-stage mycosis fungoides. The infiltrate is positively labelled with a pan-T cell marker. These are predominantly $CD4^+$ T cells.

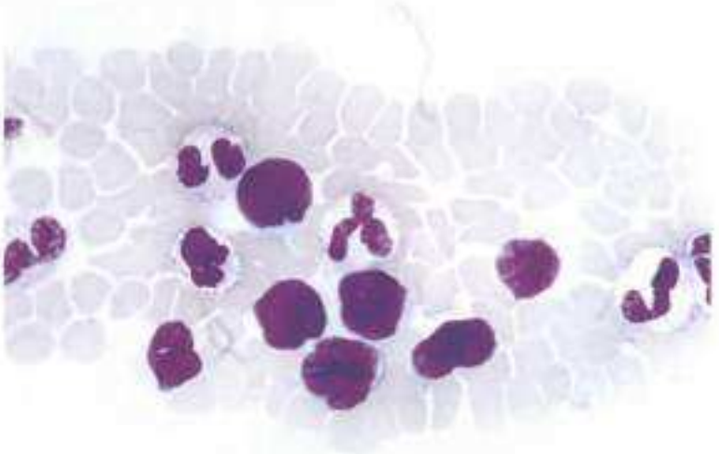


Fig. 12.22 Mycosis/Sézary cells. Cerebriform, hyperchromatic nuclei are present in the peripheral blood smear (Giemsa stain) of patients with Sézary syndrome.

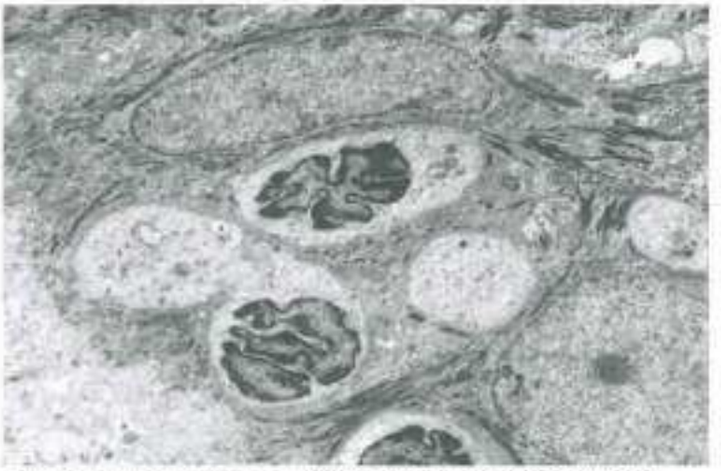


Fig. 12.23 Mycosis fungoides. These mycosis/Sézary cells have abundant cytoplasm and centrally located, irregular, highly convoluted nuclei that show peripheral chromatin distribution, shown in the electron micrograph.

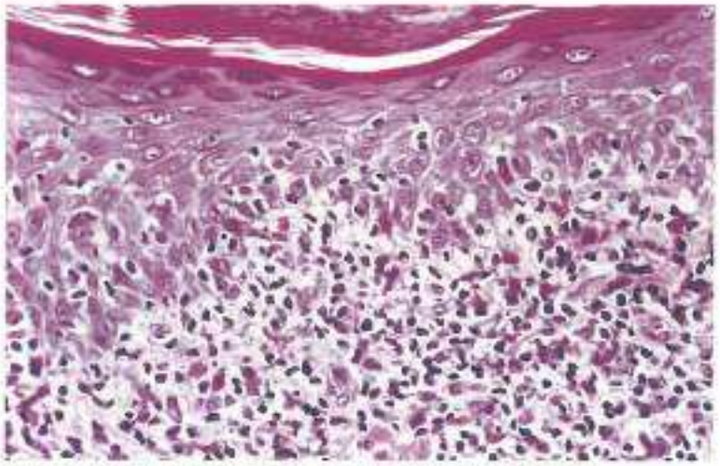


Fig. 12.24 Patch-stage mycosis fungoides. There is parakeratosis, hyperorthokeratosis and acanthosis. The epidermis and dermis are diffusely infiltrated by large numbers of cells with highly irregular, darkly staining nuclei (mycosis cells).

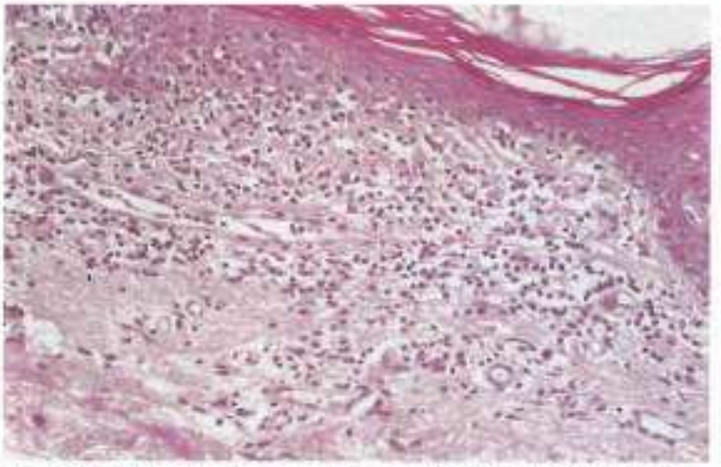


Fig. 12.25 Poikiloderma atrophicans et vasculare. There is a lichenoid band of atypical mononuclear cells in the dermis, which is infiltrating the epidermis. There are hyperkeratosis, epidermal atrophy and ectatic blood vessels in the dermis.

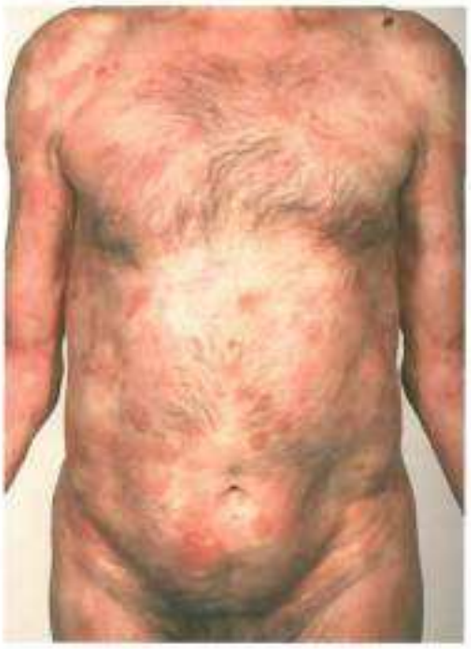


Fig. 12.26 Treatment of early-stage mycosis fungoides with psoralen plus ultraviolet A. Early-stage disease responds well to photochemotherapy.

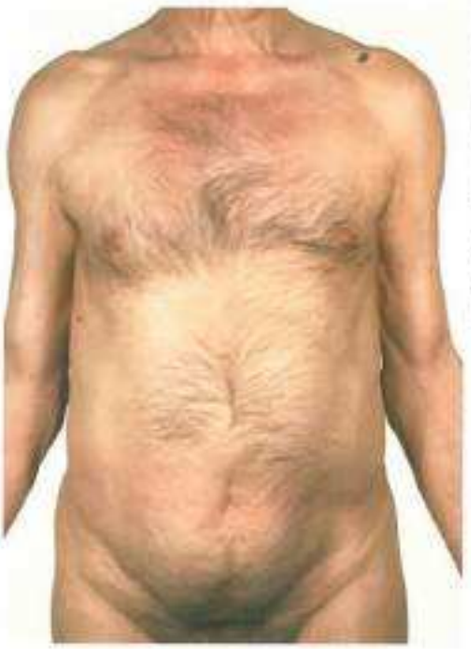


Fig. 12.27 Treatment of early-stage mycosis fungoides with psoralen plus ultraviolet A. Complete clearing of the patient in Fig. 12.26 occurred after 18 treatments. The response may be maintained with low joule exposure once a month. Skin cancer is unusual in these cases.

and confusion with other lymphomatous processes, especially Hodgkin's disease, becomes a distinct possibility. Epidermotropism is less obvious.

Poikiloderma atrophicans et vasculare is characterized by hyperkeratosis, epidermal atrophy, basal cell liquefaction degeneration and a lichenoid or perivascular superficial dermal inflammatory cell infiltrate (Fig. 12.25). Variable numbers of small, hyperchromatic, irregular lymphocytes may be found in the epithelium and dermis. Pigmentary incontinence may be a feature and telangiectatic vessels are commonly found.

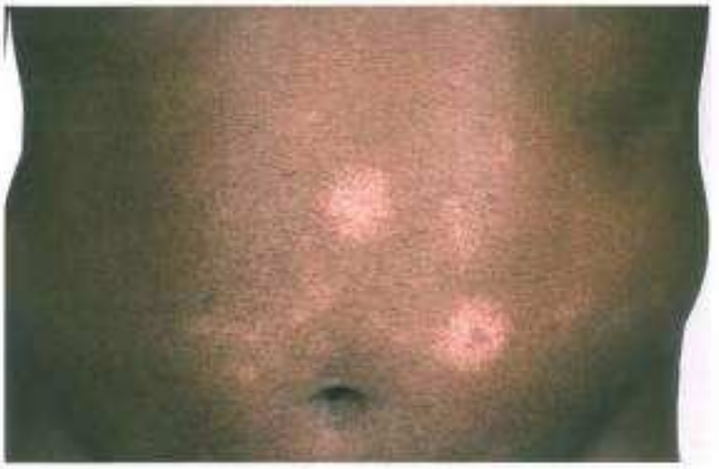
Enlarged lymph nodes may show only reactive hyperplasia or dermatopathic lymphadenopathy in early stages of both mycosis fungoides and Sézary syndrome, but with progression, destruction of the nodal architecture by typical mycosis cells becomes evident.

Management

The diagnosis is made by skin biopsy. Several are sometimes necessary in the early stages. A T (skin) N (nodes) M (viscera) B (blood) staging classification may be used where T1 is limited (<10%) and T2 widespread patches and plaques. T3 is tumour stage and T4 is erythroderma. N0 is no nodes. N1 is clinically but not histologically, N2 not clinically but histologically and N3 clinically and histologically affected. M0 is negative and M2 is positive visceral involvement. B0 is no Sézary and B1 is >5% of total in the peripheral blood. Most patients with mycosis fungoides are at stage T2 and rarely progress. Poor prognosis is related to tumours, erythroderma and lymph node involvement, where median survival is 3 years and less than one-third are alive at 5 years. The prognosis is better in dermatopathic lymphadenopathy. T cell gene rearrangement studies are usually negative; but in the LN3 and LN4 stages, they are positive and the prognosis is proportionately much worse.

Patch and plaque stage disease

Topical applications of dilute solutions of mechlorethamine (nitrogen mustard or mustine) and photochemotherapy using oral psoralens combined with long-wave ultraviolet light (PUVA) are used to clear early-stage disease (Figs 12.26 and 12.27). Both treatments are suppressive but gratifying long-term remissions may be obtained with persistent therapy



Figs 12.28 and 12.29. Hypopigmented mycosis fungoides treated with psoralen plus ultraviolet A. Hypopigmented mycosis fungoides also respond well to PUVA and repigmentation occurs with clearing of the infiltrate.

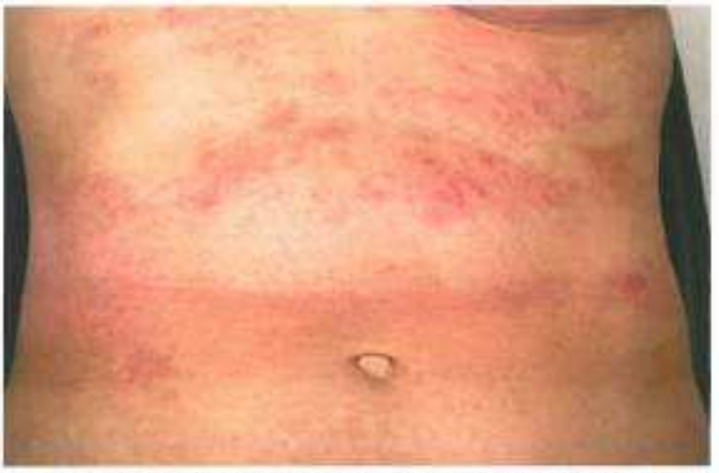


Fig. 12.30. Contact dermatitis to topical mustine. Although topical mustine is an effective treatment for early-stage mycosis fungoides, contact sensitization is common. Patients can sometimes be desensitized by gradually increasing from very dilute to standard solutions of nitrogen mustard.

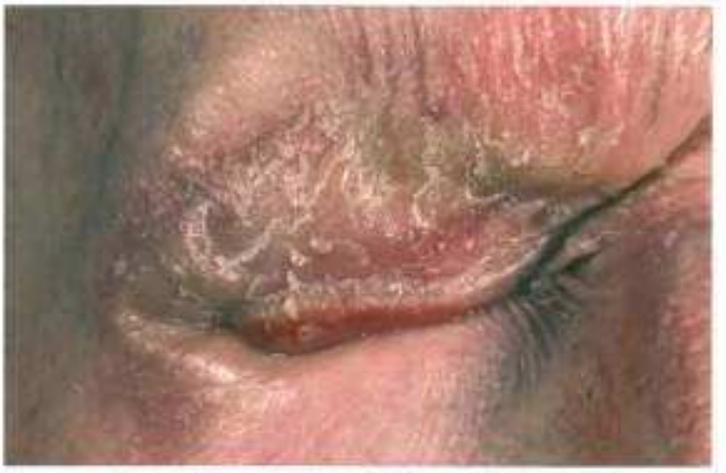


Fig. 12.31. Sanctuary site disease. During treatment with psoralen plus ultraviolet A, mycosis fungoides may occur in shielded sites, such as the groin, axillae or, as in this case, the eyelids, which were covered by protective glasses. These areas may be cleared with topical mustine.

(Figs 12.28 and 12.29). Topical mechlorethamine does cause contact dermatitis (Fig. 12.30) in 40% of patients but most can easily be desensitized. It can be applied at home and can be used to treat areas of the skin that are sheltered from ultraviolet irradiation (Fig. 12.31). Photochemotherapy may be used alone or combined with topical mechlorethamine. Both treatments have the disadvantage that they are cutaneous carcinogens (Fig. 12.32), although all complicating lesions reported so far have been amenable to treatment.

Tumour-stage mycosis fungoides

This is usually managed with localized radiotherapy or, if lesions are widespread, with electron beam irradiation. Some centres have advocated radical therapy from the start, following the major advances that have been made in the aggressive treatment of Hodgkin's disease. They have suggested whole-body electron beam therapy and systemic treatment with cytotoxic drugs. However, since the condition is so variable in its behaviour and is benign in the majority of patients, it is difficult to assess the results and it is questionable whether whole-body irradiation is justifiable in every case.

Various systemic agents have been used including interferon , retinoids, methotrexate, pegylated liposomal doxorubicin and combination

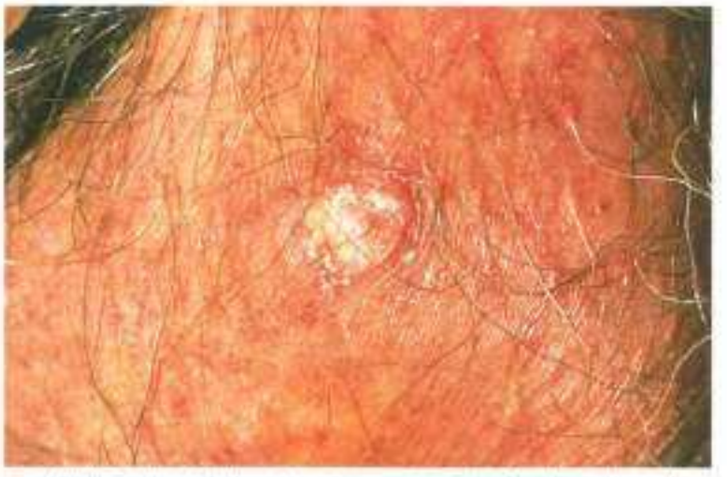


Fig. 12.32. Treatment-induced carcinogenesis. Topical mustine and psoralen plus ultraviolet A are known carcinogens. This early squamous cell carcinoma of the scrotum developed after a decade of mustine therapy, but it is a rare complication. (Courtesy of Dr E. van Scott.)

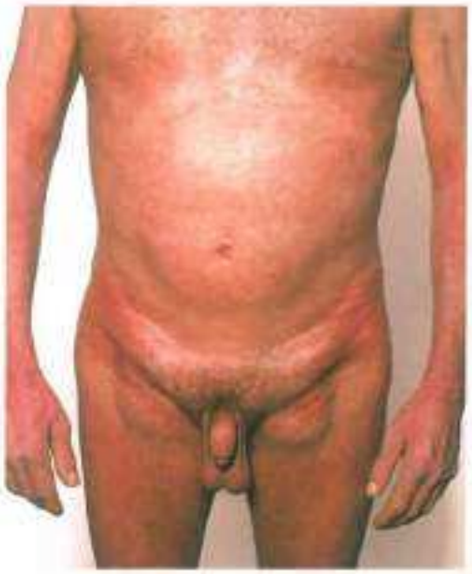


Fig. 12.33 Sézary syndrome. Note the inguinal lymphadenopathy. He ultimately succumbed to overwhelming sepsis. (Courtesy of St Mary's Hospital.)

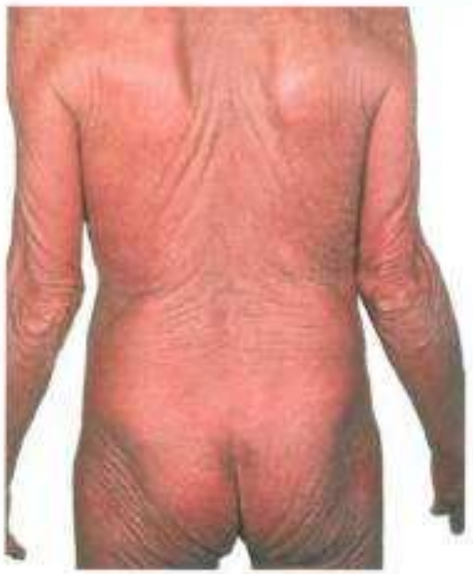


Fig. 12.34 Sézary syndrome. The condition results in a universal redness of the skin (erythroderma), with the most intractable and distressing pruritus.

chemotherapeutic regimens using cyclophosphamide, methotrexate, etoposide and dexamethasone (CMED) alternating with adriamycin, bleomycin and vincristine (ABV). They all show some efficacy but do not greatly increase survival and the combination regimen is not without its side-effects.

Newer agents include:

- **Bexarotene** This agent is selective for the retinoid X receptors unlike traditional retinoids which have a receptor for retinoic acid receptors. There is a variable response time. All become hypothyroid and hyperlipidaemic.
- **Denileukin difitox (Ontak)** This is a targeted IL-2 fusion protein which induces apoptosis.
- **Histone deacetylase inhibitors** These include Vorinostat and Depsipeptide. They result in accumulation of acetylated proteins which lead to changes in gene expression. They reduce oncogene expression and increase suppressor gene expression and therefore cell cycle arrest and apoptosis. They are given intravenously. Nausea and prolongation of the QT interval are common side-effects.

Peripheral stem cell transplantation and other forms of marrow transplantation have been tried but are generally disappointing.

Sézary syndrome

An intensely pruritic erythrodermic variant of mycosis fungoides with lymphadenopathy secondary to a malignant proliferation of $CD4^+$ T helper cells in the skin and peripheral circulation, with relative lymphopenia or abnormal T cells leading to immunoparesis.

Aetiology

In 1892, Besnier and Hallopeau described a red man (l'homme rouge) who appeared to have an erythrodermic variant of mycosis fungoides. In 1938, Sézary and Bouvrain reported a case of erythroderma, intense pruritus, lymphadenopathy and cellules monstreuses in the peripheral blood. In 1968, Lutzner and Jordan demonstrated the presence of cells with nuclei having a serpentine, or highly convoluted, cerebriform ultrastructure. These cells were subsequently identified as malignant T helper cells. They are the same as in mycosis fungoides and the majority are $CD45^+Ro45^+CD4^+$ memory T helper cells. Based on the cytokines expressed by these cells, it has been suggested that mycosis fungoides exhibits a TH1 profile and Sézary syndrome a TH2 profile. Other cell markers may be expressed including $CD8^+$ (suppressor T cell) and sometimes CD25 (interleukin 2 receptors). Southern blotting and the polymerase chain reaction have established the monoclonal nature of the malignant T cells infiltrating the skin, lymph nodes and blood in both Sézary syndrome and advanced mycosis fungoides. Sézary cells may be found in the bone marrow but not always and certainly not in large numbers, suggesting that the disorder does originate from the skin.

Clinical Features

Symptoms

Pruritus is extremely distressing.

Morphology

It begins insidiously with patches, like mycosis fungoides, and is usually diagnosed as a drug eruption, psoriasis or eczema, but it fails to respond to therapy and spreads, eventually resulting in universal involvement of the skin, lymphadenopathy (Fig. 12.33) and visceral involvement. Once the erythroderma is established, there is oedema and thickening of the skin, which has a tendency to hang in folds (Fig. 12.34). The face may then have a leonine appearance, and ectropion may be a marked feature. There is a palpable erythema, hyperkeratosis and fissuring of the palms (Fig. 12.35) and soles, with marked onychodystrophy (Fig.

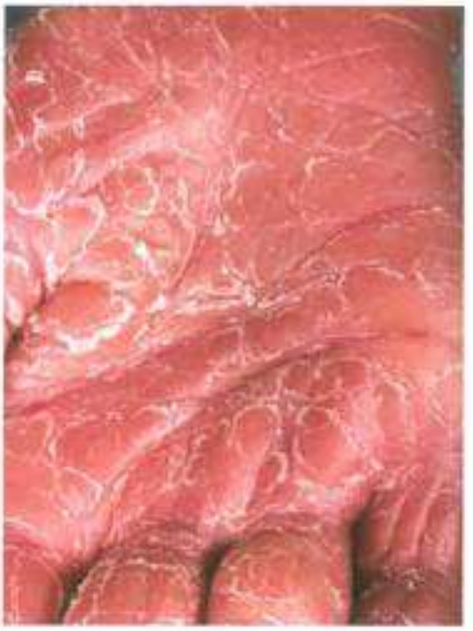


Fig. 12.35 Sézary syndrome. The palms and soles are usually diffusely involved. The skin is red, thickened and hyperkeratotic.

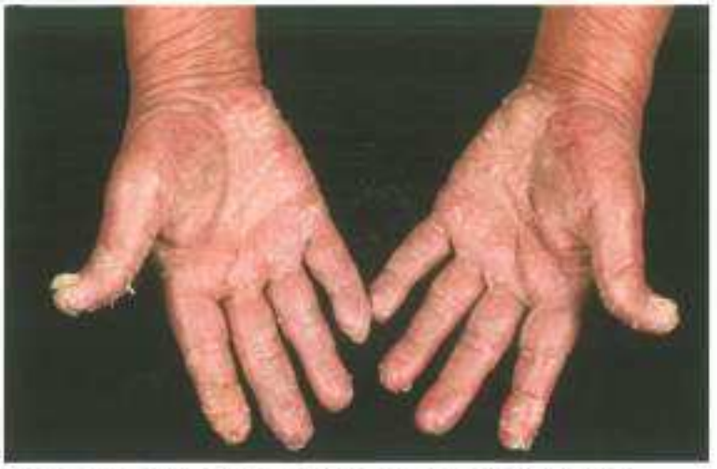


Fig. 12.36 Sézary syndrome. The palms and soles are characteristically thickened, scaly and fissured. The nails are also involved.

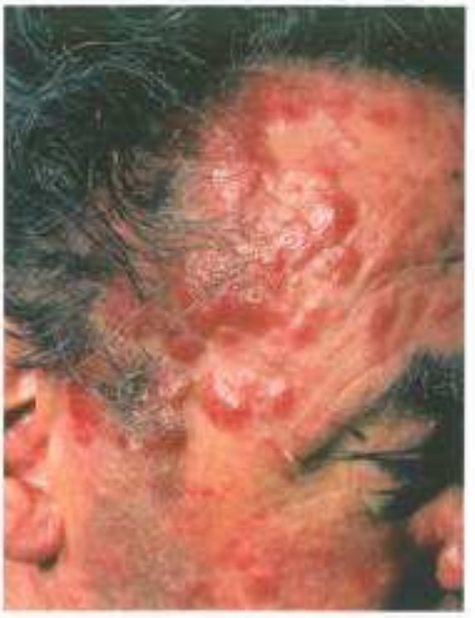


Fig. 12.37 Sézary syndrome. As the disease progresses, tumours may occur on the face. This is an ominous sign. (Courtesy of St Mary's Hospital.)

12.36). As the disease progresses, tumours may develop on the skin, particularly on the face and the scalp (Fig. 12.37).

Distribution

The whole integument is involved including palms and soles. The hair and nails are often lost.

Management

Other causes of erythroderma (eczema, psoriasis, pityriasis rubra pilaris, drug eruptions, sarcoidosis, HTLV-1 and paraneoplastic phenomena) should be excluded by skin biopsy (Fig. 12.38), peripheral blood count, lymph node biopsy, bone marrow biopsy and other staging procedures.

The prognosis is variable. Some patients enjoy tolerable health for a number of years before generalized involvement of the reticuloendothelial system and skin tumour formation occur. Indeed, some patients, although erythrodermic, never, or only latterly, develop obvious Sézary cells in the peripheral blood and marrow; the disease is then referred to as either pre-Sézary syndrome or *erythrodermic mycosis fungoides*. Others eventually die, usually secondary to overwhelming infections, often staphylococcal or pseudomonal, sometimes starting at the sites of indwelling catheters.

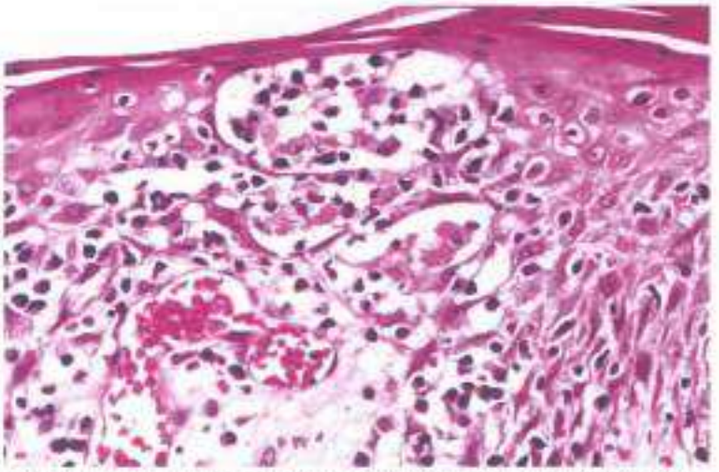


Fig. 12.38 Sézary syndrome. There is epidermal infiltration by large numbers of Sézary cells, resulting in several Pautrier abscesses. A congested dilated blood vessel is situated just below the epithelium on the left side of the picture.

Treatment is unsatisfactory and is similar to that of systemic mycosis fungoides. Sézary syndrome differs from mycosis fungoides in showing a limited or no response to photochemotherapy or topical mechlorethamine. Electron beam therapy may give short-term relief.

Chemotherapy

Bexarotene, Ontak and HTAC inhibitors are being trialled in the same manner as for tumour stage mycosis fungoides.

Extracorporeal photophoresis

Extracorporeal photophoresis is however an important treatment. Patients undergo leucophoresis. The buffy coat lymphocytes are isolated, bathed in 8-methoxypsoralen, passed through a thin plastic exposure plate, irradiated with ultraviolet A and returned intravenously. The technique may be temporarily effective, indicating that there is a dynamic equilibrium between the skin and the blood. The best results are seen in those with early disease where there are normal CD4/CD8 cell ratios.

Lymphomatoid papulosis

An essentially benign $CD30^+$ T cell lymphoma, which occasionally becomes malignant. It is characterized by recurrent crops of red-brown papules or nodules on the trunk and limbs that spontaneously regress by crusting, necrosis and scarring.

Aetiology

First described clinically by Macaulay in 1968, it is now recognized to be a $CD30^+$ T cell disorder. There are three subtypes which depend on the number of atypical $CD30^+$ cells present. Type A resemble the Reed–Sternberg cells of Hodgkin's disease and express CD30 (Ki-1) antigen. Type B are $CD30^-$, cerebriform hyperchromatic cells resembling those of mycosis fungoides with a band-like dermal infiltrate and epidermotropism. Type C resembles type A, but there are large clusters of $CD30^+$ atypical lymphocytes (greater than 50%) in sheets or large nodules simulating anaplastic large cell lymphoma. These distinctions are however not always so well cut. The atypical cells do express a T cell phenotype and the condition is thought to be a T cell lymphoproliferative disease, probably a pseudolymphoma if not a low-grade lymphoma, particularly because possibly 10% develop mycosis fungoides, $CD30^+$ large cell lymphoma, T cell immunoblastic lymphoma or Hodgkin's disease. The disease has a

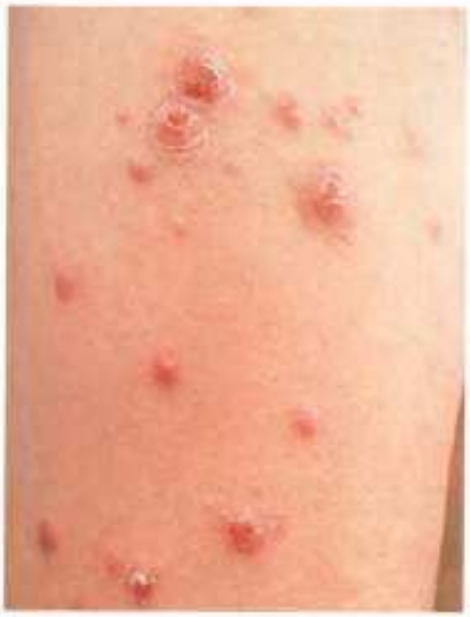


Fig. 12.39 Lymphomatoid papulosis. The lesions are at different stages of development and consist of recurrent crops of red-brown indurated papules and nodules that regress with crusting, necrosis and scarring. The histology appears aggressive but the course is essentially benign.

benign course, however, in most patients and in some simulates pityriasis lichenoides. The cause is unknown. Epstein–Barr virus, which is implicated in such disorders as Burkitt's lymphoma, $CD30^+$ anaplastic lymphoma and Hodgkin's disease, appears to be exonerated at the present time, but lymphomatoid papulosis may still be a viral disorder, not least because HTLV-1 is implicated in adult T cell leukaemia/lymphoma and is known to upregulate CD30.

Lymphomatoid papulosis occurs in all races. It may commence at any time but usually around the fifth decade.

Clinical Features

Symptoms

There are recurrent, self-healing spots on the skin.

Morphology

Recurrent erythematous papules or nodules occur that soon become haemorrhagic, crusted and necrotic (Fig. 12.39) and heal with scarring. The lesions appear in groups or singly.

Distribution

Predominantly on the trunk and extremities.

Histopathology

The fully established lymphomatoid papule has a rather characteristic dense pleomorphic, mitotically active, wedge-shaped infiltrate (with its broad base uppermost) that extends from the epidermis often into the superficial aspects of the subcutaneous fat (Fig. 12.40). The infiltrate consists of an admixture of polymorphs, eosinophils, plasma cells, Langerhans' cells and variably differentiated lymphoid cells (Fig. 12.41). The last includes many bizarre forms such as immunoblasts. The epidermis is acanthotic and parakeratotic. Endothelial swelling and diapedesis of red blood cells both in the dermis and epidermis are the rule.

Management

Skin biopsy and immunostaining are necessary for diagnosis. However, despite its worrying histopathology, the results of extensive clinical investigations for systemic involvement are usually negative. Pityriasis lichenoides chronica enters the differential diagnosis clinically but has a different histology. Although in most cases the course is benign, the patient should be followed long term because of the occasional association with lymphoma. The individual lesions respond to photochemotherapy, low-dose methotrexate or etretinate.

Follicular mucinosis

A rare follicular variant of mycosis fungoides.

Aetiology

First described by Pinkus in 1957 and called *alopecia mucinosa* (because of the specific histological abnormality of mucinous follicular degeneration), there is infiltration of follicular epithelium by atypical lymphocytes. It differs from classical mycosis fungoides by frequently involving the head and neck with comedone-like, cystic and acneiform lesions in addition to infiltrated plaques and sometimes having a more aggressive course. T cell gene rearrangement studies are consistent with a clonal T cell lymphoproliferation. Follicular mucinosis occurs in both sexes (particularly males) and may start at an early age.

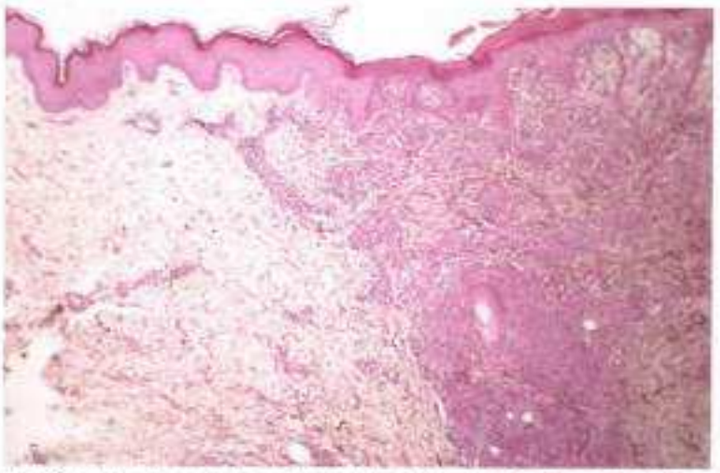


Fig. 12.40 Lymphomatoid papulosis. Low-power view showing an ulcerated papule with a wedge-shaped heavy inflammatory cell infiltrate.

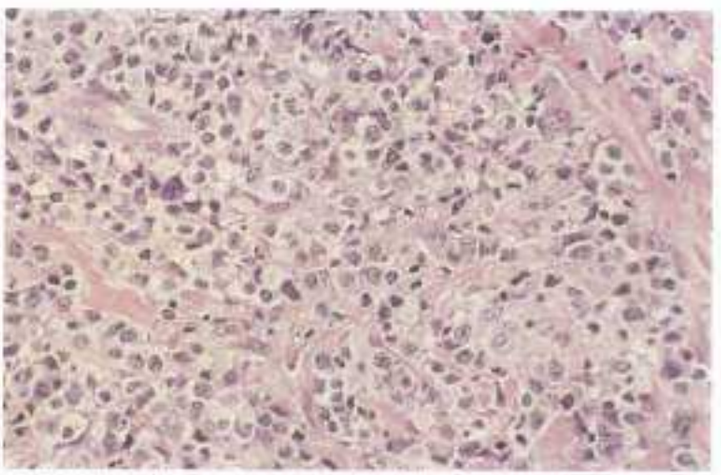


Fig. 12.41 Lymphomatoid papulosis. The infiltrate is polymorphic. Plasma cells and lymphocytes are mixed with larger cells with abundant cytoplasm, irregular vesicular nuclei and prominent nucleoli. Mitotic figures are present.

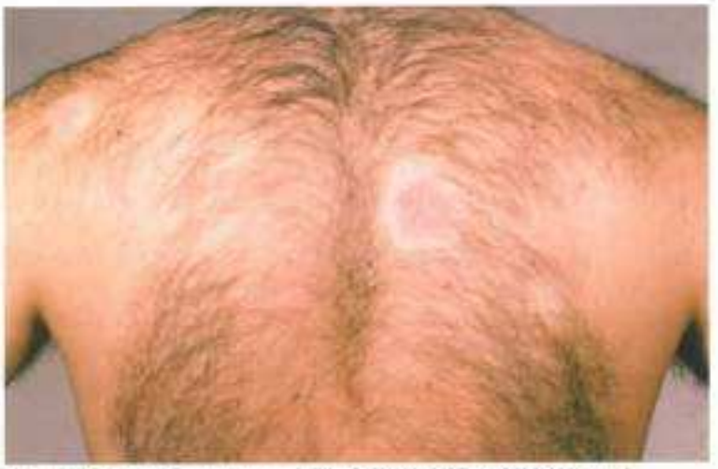


Fig. 12.42 Follicular mucinosis. Red infiltrated plaques are present with alopecia. Biopsy is necessary to establish the diagnosis.

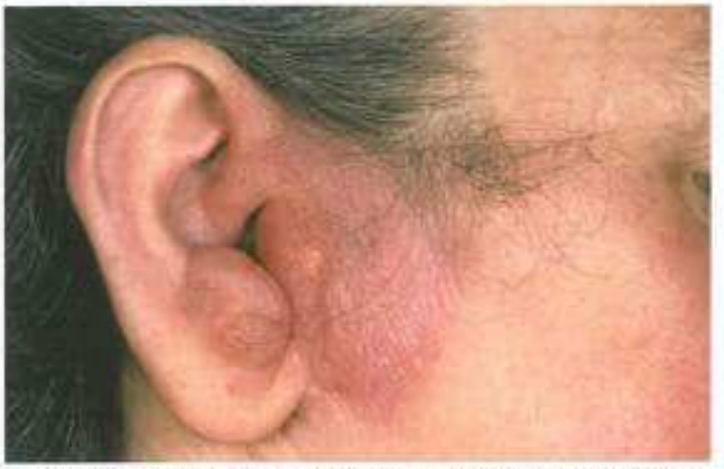


Fig. 12.43 Follicular mucinosis. A thickened, well-defined, oedematous plaque is present in and around the ear. The head and neck are the usual sites for limited forms of the disease. (Courtesy of Dr D. Volkum.)

Clinical Features

Symptoms

There are patches on the skin with associated hair loss (Fig. 12.42).

Morphology and distribution

Three variants of follicular mucinosis are traditionally described; however, with modern immunotyping and gene rearrangement studies these are becoming less distinct. Prognosis and management should be based on these techniques rather than distribution. However, the most common type is confined to the head and neck region and affects the hair-bearing areas, such as the beard, eyebrows or scalp, with resultant hair loss. The lesions are well-defined, infiltrated, red plaques (Fig. 12.43). Occasionally, a mucinous material may be expressed from the hair follicles, which are usually prominent and patulous. The condition may remit after a couple of years. The second variety is similar clinically but much more extensive; it occurs in an older age group. It may also resolve, but the process takes longer. The third appears to be a variant of mycosis fungoides and the diagnosis is suspected because there may be typical patches of mycosis fungoides or poikiloderma, interspersed with extensive follicular mucinosis.

Histopathology

The appearances are those of mucinous degeneration involving the sebaceous glands and the external root sheath of the hair follicles (Fig. 12.44). Acid mucopolysaccharides are present, which stain positively with Alcian blue. In the third variant, the changes of mycosis fungoides are superimposed.

Management

A biopsy is necessary for confirmation of the diagnosis. The localized varieties of follicular mucinosis may be treated with radiotherapy. The extensive disorder is treated like mycosis fungoides.

Fig. 12.44 Follicular mucinosis. Intercellular deposition of mucin results in the vacuolated appearance of the follicular epithelium. The chronic inflammatory cell infiltrate is non-specific in this example. Not all cases show mucin degeneration.

Adult T cell leukaemia/lymphoma

Adult T cell leukaemia/lymphoma causes skin lesions that simulate mycosis fungoides and the Sézary syndrome, both clinically and histologically. It is associated in most cases with HTLV-1 infection.

Aetiology

The majority of patients with T cell leukaemia/lymphoma are middle-aged or older and carry the HTLV-1 virus integrated into the genome of the neoplastic T cells (helper/inducer phenotype). This induces transcription of interleukin 2 and its receptor ($CD25^+$) and causes polyclonal proliferation of infected cells. HTLV-1 is common in Southern Japan, sub-Sahara Africa, the Caribbean and the southeastern USA. It is transmitted by breast-feeding, sexual intercourse, blood transfusion and contaminated needles. The lifetime risk of developing adult T cell leukaemia in those infected with HTLV-1 is about 4%, which results in a skin eruption, hypercalcaemia, lymphadenopathy, hepatosplenomegaly, involvement of the lungs and central nervous system and opportunistic infections. The virus is also responsible for most cases of Norwegian scabies in the West Indies and also causes an infective dermatitis in Jamaican children.

Clinical Features

In adult T cell leukaemia/lymphoma there is an itchy rash.

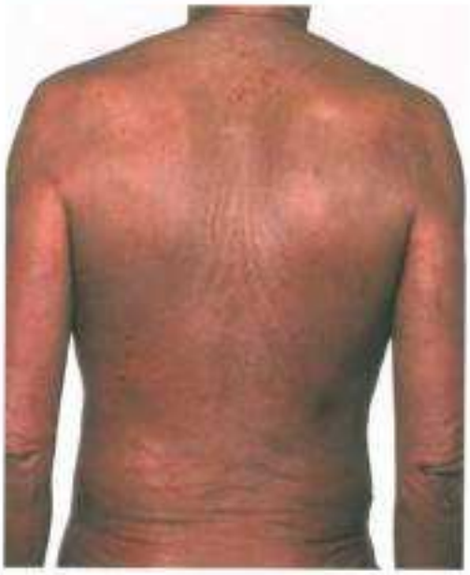


Fig. 12.45 Adult T cell leukaemia/lymphoma. Although the redness of the erythroderma can be difficult to visualize in black skin it is visible here. The skin is beginning to hang in folds. This man was positive for human T cell leukaemia/ lymphoma virus type 1.

Fig. 12.46 Adult T cell leukaemia/lymphoma. Note the excoriations. Itching is intractable and immensely distressing. Whole-body electron beam therapy and Daclizumab gave the patient (Fig. 12.45) temporary relief, but he still succumbed.

Morphology

The lesions are papules, plaques, nodules, tumours and ulcers and in many respects simulate the cutaneous changes of mycosis fungoides. There may be erythroderma (Figs 12.45 and 12.46) or an acquired ichthyosis.

Distribution

The lesions particularly occur on the trunk and limbs.

Management

The diagnosis of adult T cell leukaemia/lymphoma can be established by skin biopsy initially but also by biopsy of the lymph nodes. The histopathology is similar to mycosis fungoides and Sézary syndrome. The full blood count will reveal the diagnosis. The patient will be HTLV-1 positive if they come from an endemic area but is likely to be negative in Europe and in many states in the USA. There are various clinical subtypes including an acute variety, with circulating leukaemic T lymphocytes and tumour formation, and a lymphoma variant; both are aggressive and have a poor prognosis. There are, however, smouldering and chronic varieties that fare better, although bacterial infections are common. Treatment is unsatisfactory but has included interferon α, zidovudine, etretinate, anti-CD25 antibodies conjugated to yttrium 90 and stem cell transplantation.

Other cutaneous T cell lymphomas

The following are exceptionally rare CTCLs:

- *Granulomatous slack skin disease* is characterized histologically by a dense granulomatous infiltrate of abnormal helper T lymphocytes, which exhibit epidermotropism but also cause destruction of dermal elastic tissue (elastolysis; Fig. 12.47) and result in pendulous folds of lax erythematous skin, particularly in the flexures (Fig. 12.48). It occurs in adolescence and middle-age, is indolent but can progress to Hodgkin's disease or non-Hodgkin's lymphoma.

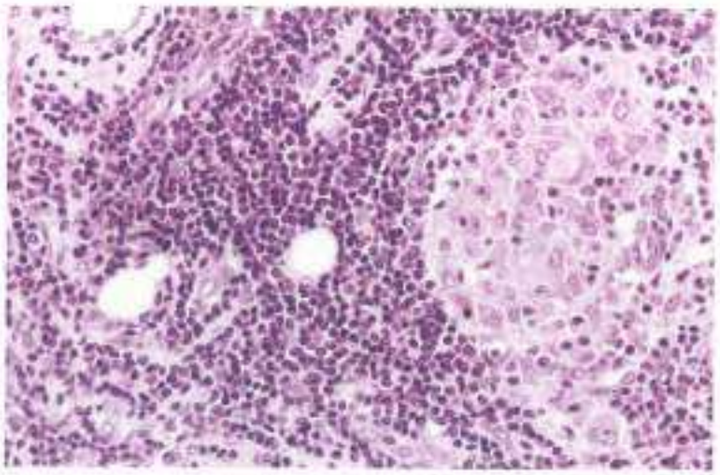


Fig. 12.47 Granulomatous slack skin disease. There is a granulomatous infiltrate with destruction of elastic tissue. The lymphocytes are abnormal helper T cells.

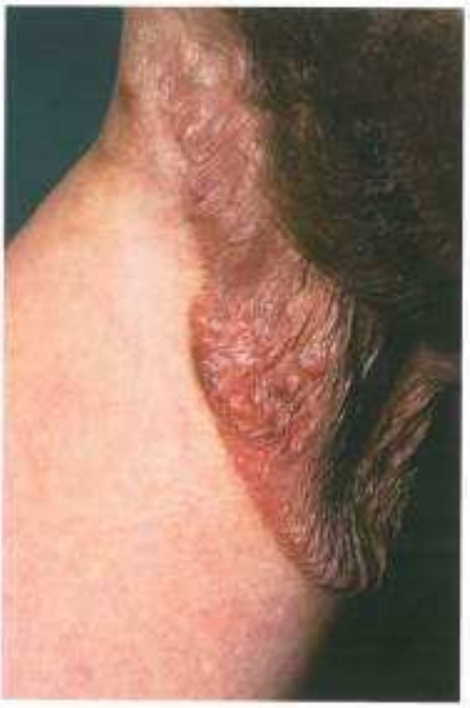


Fig. 12.48 Granulomatous slack skin disease. The granulomatous abnormal T cell infiltration destroys the elastic tissue and causes the skin to hang in pendulous lax folds in the flexures. (With permission from Bolognia JL, Jorizzo JL, Rapini RP, et al: Dermatology, 2nd edition. London: Elsevier, 2008.)

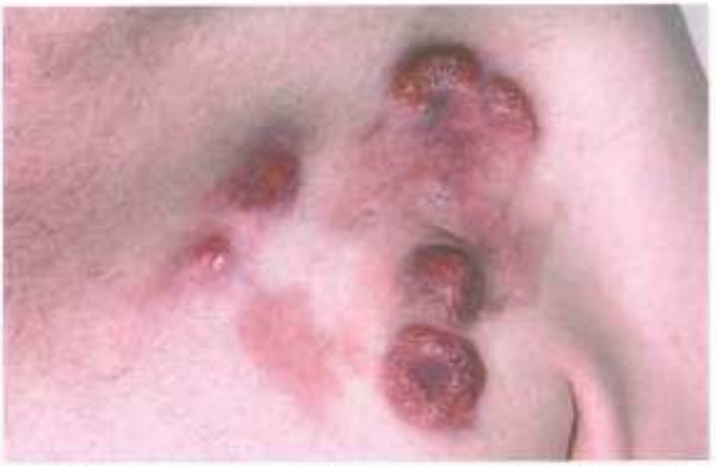


Fig. 12.49 Primary cutaneous CD30$^+$ large cell lymphoma. There are plum-coloured nodules. The prognosis is good, unlike in CD30$^-$ lymphomas. (Courtesy of Dr Daniel Creamer.)

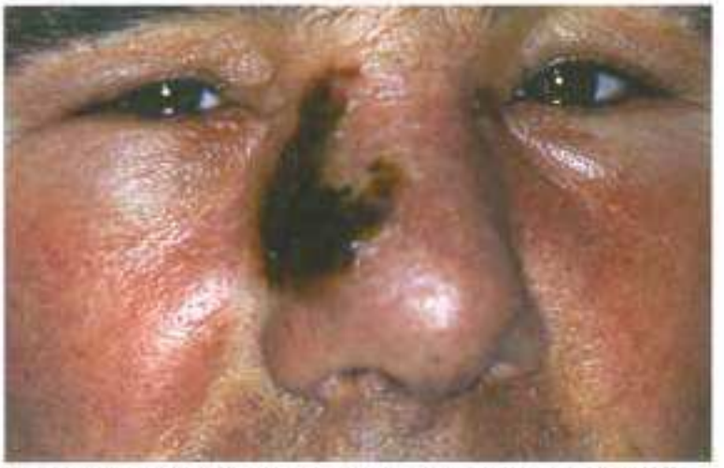


Fig. 12.50 Extranodal NK/T cell lymphoma, nasal type. This Epstein–Barr-driven aggressive lymphoma may present on the skin with naso-facial deformative ulcerative tumours. (Courtesy of Dr Michèle Clement.)

- *Primary cutaneous CD30$^+$ large-cell lymphoma* (Fig. 12.49) is characterized by large anaplastic cells with abundant cytoplasm, often with eosinophilic nucleoli, and a peripheral reactive infiltrate of small benign lymphocytes in the papillary and reticular dermis. It does not exhibit the epidermotropism that is so characteristic of other T cell disorders. Unlike CD30$^+$ lymphomas affecting lymph nodes, the prognosis is good and the tumours respond to radiotherapy.
- *CD30$^-$ cutaneous T cell lymphoma* (now part of a category called primary cutaneous peripheral T cell lymphoma, unspecified) probably represents the tumeur d'emblée described by Brock. There is a sudden appearance of nodules without preceding plaques, these nodules are often multiple and recur. There is little epidermotropism, but large, medium or small pleomorphic T lymphocytes are present. The lesions are radiosensitive but the prognosis is guarded.
- *Extranodal NK/T cell lymphoma nasal type.* This is an EBV driven aggressive lymphoma with a natural killer T cell or cytotoxic T cell phenotype. Previously known as lethal midline granuloma it is a midfocal destructive ulcerative tumorous condition (Fig. 12.50). The trunk and extremities may also be involved and throat and extranasal deposits (spleen, liver, nodes, CNS and testis) are common. Patients may have the haemophagocytic syndrome. It is very rare but more common in Asian and Central or Southern American males than Europeans.
- *Primary cutaneous aggressive epidermotropic CD8$^+$ cytotoxic T cell lymphoma.* Previously named *disseminated Pagetoid reticulosis of Ketron–Goodman,* it is characterized by eruptive papules, nodules and tumours which may ulcerate and be diagnosed on the pathological findings referred to in its new name. It is very rare and aggressive.
- *Primary cutaneous CD4$^+$ small/medium sized pleomorphic T cell lymphoma.* This lymphoma differs clinically from mycosis fungoides because it is usually a solitary plaque or tumour on the head and neck or trunk with the histological and immunostaining characteristics referred to in the title. It has a good prognosis.
- *CD4$^+$/CD56$^+$ haematodermic neoplasm* (plasmacytoid dendritic cell neoplasm). This is a clinically distinctive highly aggressive lymphoma probably derived from a plasmacytoid dendritic cell precursor which is often mistakenly thought to be related to myelodysplastic syndrome or acute myeloid leukaemia. Extensive tumours (Fig. 12.51) develop on the torso (and may involve the head and face) with a purple or bruise-like hue (Fig. 12.52). The bone marrow, lymph nodes and extra-nodal sites are often involved. CD4, CD56 and CD125 immunostaining is positive in all tissues. At present, early bone marrow transplantation is the preferred option for this otherwise mortal disease.
- *Subcutaneous panniculitis-like T cell lymphoma* is very rare and presents with tumours often localized to the limbs (Fig. 12.53). Epidermotropism is

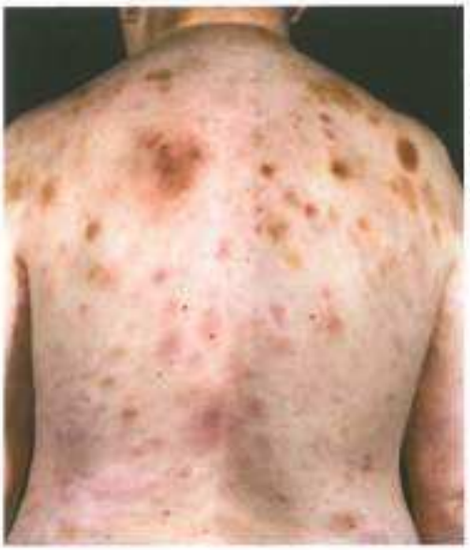


Fig. 12.51 Plasmacytoid dendritic cell neoplasm. There are multiple tumours affecting all areas (including the face and scalp) which become brown and simulate a bruise.

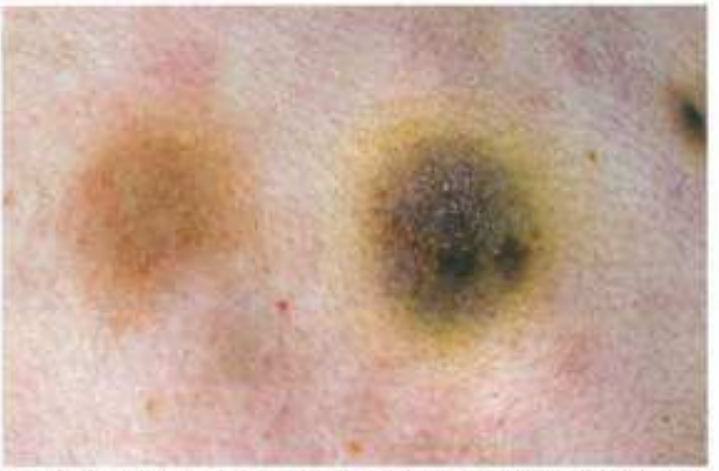


Fig. 12.52 Plasmacytoid dendritic cell neoplasm. The bruise-like appearance of the tumours is virtually diagnostic. There is lymphadenopathy and the blood picture may simulate myelodysplastic syndrome or acute myeloid leukaemia.

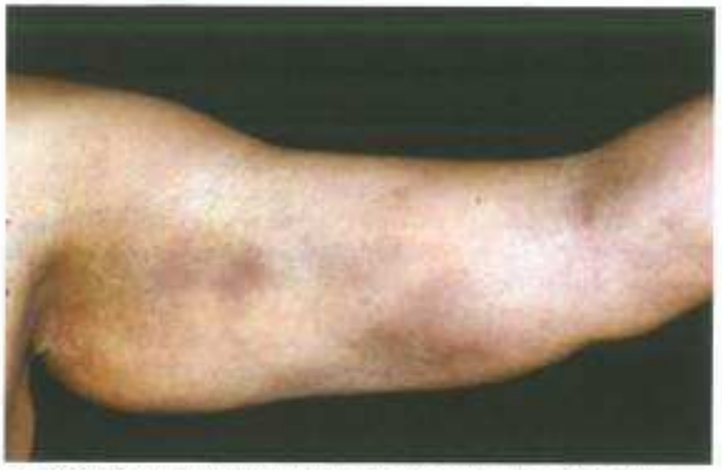


Fig. 12.53 Subcutaneous panniculitis-like T cell lymphoma. The lesions stimulate a panniculitis but there are B symptoms (night sweats, weight loss, anaemia and malaise). The diagnosis is made by biopsy. (Courtesy of Dr Andrew Pembroke.)

minimal and the atypical T cells are angiocentric and are found deep in the dermis, subcutaneous tissue and fat; it may resemble a panniculitis. The condition may overlap with angiocentric T cell lymphoma. There are indolent expanding nodules with systemic B symptoms of fever, night sweats, malaise and weight loss. It may progress to a haemophagocytic syndrome. Those cases with an α/β T cell phenotype have an indolent course. Those with a γ/δ T cell phenotype run an aggressive course and represent a separate entity.

B cell lymphomas

Specific involvement of the skin is rare in Hodgkin's disease, and cases so reported may have been lymphomatoid papulosis. However, generalized pruritus secondary to Hodgkin's and non-Hodgkin's lymphoma is quite common. Very occasionally, acquired ichthyosis (Fig. 12.54), hyperpigmentation or erythroderma may occur. Patients are prone to fungal (pityriasis versicolor and candidiasis) and viral infections of the skin (Fig. 12.55) since they are immunosuppressed. Herpes zoster, particularly the disseminated form, is a common complication.

Occasionally, a patient may present with tumours in the course of non-Hodgkin's lymphoma. The lesions are purple or plum-coloured (Fig. 12.56) papules, plaques, nodules or tumours (Fig. 12.57), which may or

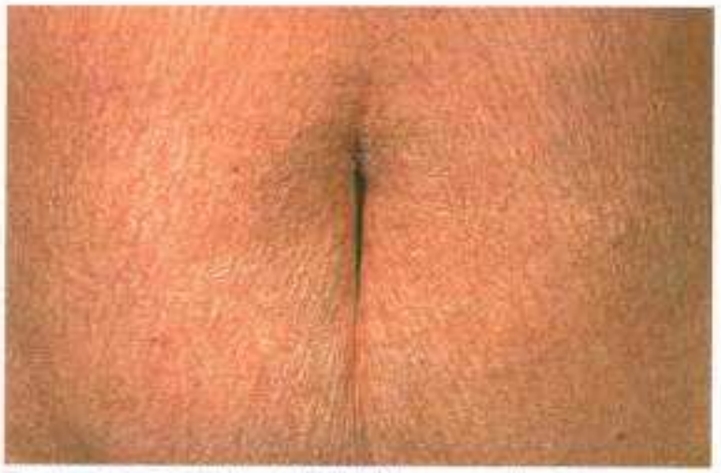


Fig. 12.54 Acquired ichthyosis. Hodgkin's disease occasionally presents as acquired dry skin. (Courtesy of the late Dr R. H. Marten.)

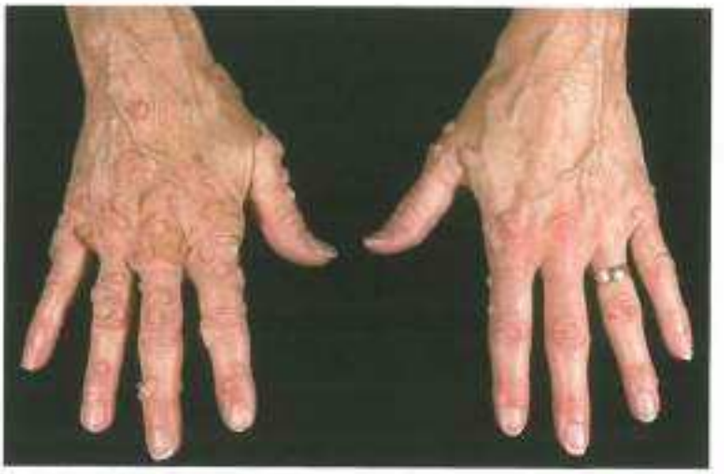


Fig. 12.55 Disseminated warts. This patient presented with widespread warts. Full blood count was normal but she had a low $CD4^+$ cell count and a bone marrow biopsy demonstrated chronic lymphatic leukaemia.

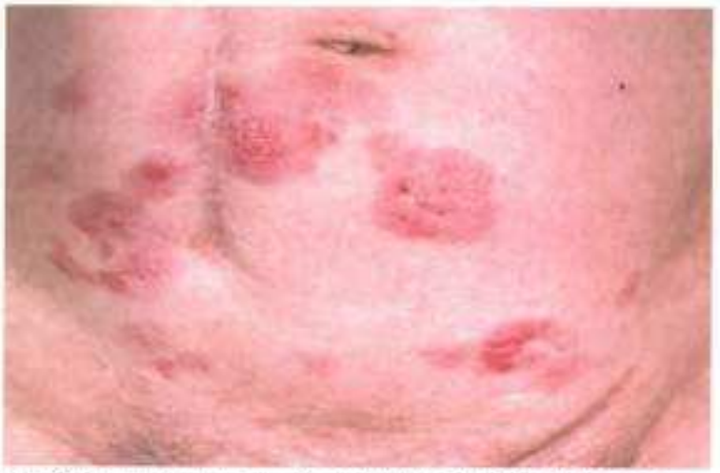


Fig. 12.56 Non-Hodgkin's lymphoma. Infiltrated plum-coloured plaques are present. Skin biopsy is essential.

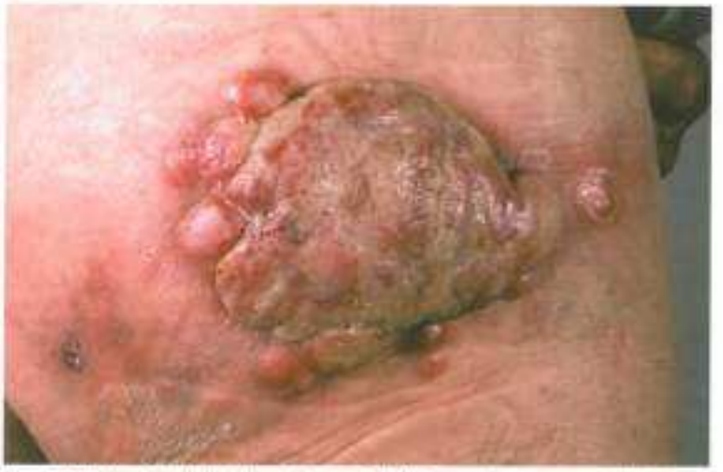


Fig. 12.57 Non-Hodgkin's lymphoma. This 75-year-old man presented with a large tumour on the buttock. It responded to six courses of CHOP.

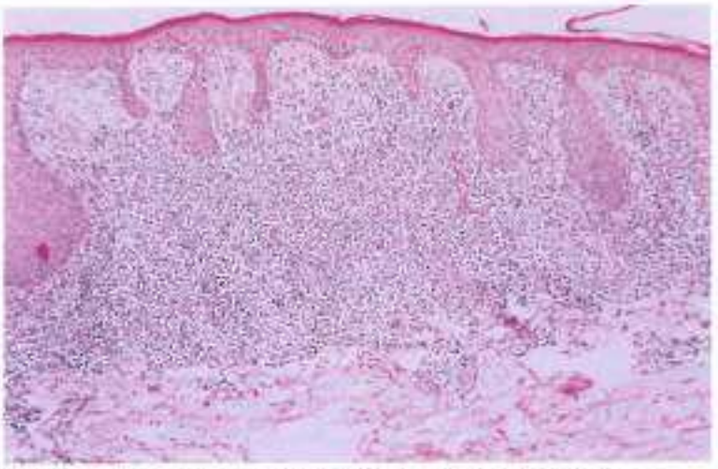


Fig. 12.58 B cell lymphoma. The epidermis is uninvolved. A Grenz zone is present. A dense band-like infiltrate occupies the upper and mid-dermis.

may not ulcerate. The lesions have the characteristics of the original lymphoma both histologically and immunophenotypically. There is a dermal infiltrate of malignant-appearing lymphocytes that extends into the subcutaneous fat. There is usually a characteristic sparing of the uppermost portion of the dermis, the so called Grenz zone (Fig. 12.58). This is in marked contrast to mycosis fungoides, where the infiltrate is in the upper part of the dermis and infiltrates the epidermis. The lymphocytes of non-Hodgkin's lymphoma are usually derived from the bone marrow (B cells) as opposed to the thymus-derived lymphocytes (T cells) of mycosis fungoides. The prognosis is that of the systemic lymphoma.

Primary cutaneous B cell lymphomas are a form of non-Hodgkin's disease lymphoma which after complete investigation are found to be confined to the skin. They tend to occur in middle age and affect both sexes equally and present as nodules or tumours at any site on the skin.

There are no data on specific genetic features such as 14:18 translocations as seen in nodal non-Hodgkin's lymphoma. Some centres have found evidence of *Borrelia* infection prompting comparisons with *Helicobacter pylori* and MALT lymphomas of the gut mucosa suggesting chronic antigenic stimulation. EBV and HHV7 and 8 studies have been negative. HIV infections have been associated particularly with the rare plasmablastic lymphomas. Classification by the WHO and EORTC is complex but is partly based on the anatomical zone of origin in the lymph node: margin, mantle or follicle centre.

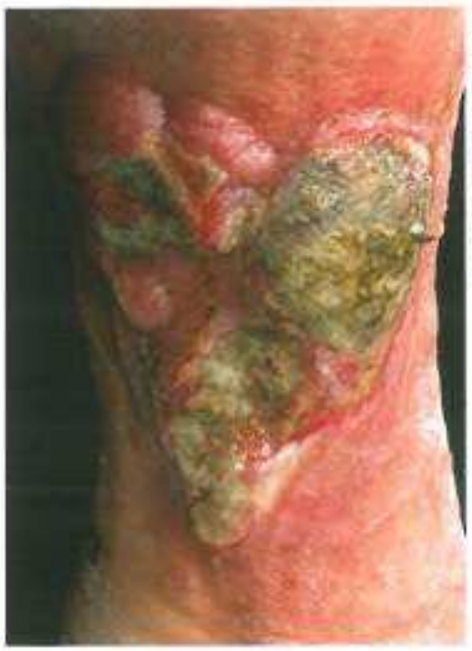


Fig. 12.59 Large B cell lymphoma of the leg. This is a condition comprising tumours on the leg associated with lymphoedema. It affects the elderly. Unlike other follicular centre tumours, the prognosis is guarded. (Courtesy of Dr Robin Russell-Jones.)

- *Primary cutaneous follicular centre cell lymphoma* is the most common. There is a heavy lymphocytic infiltrate in the reticular dermis and subcutaneous fat with a clear Grenz zone in the papillary dermis. Large lymphocytes include cells with cleaved (centrocytes) and non-cleaved (centroblasts) nuclei that are characteristically found in the follicle centres of the lymph nodes. There is bcl-6 positivity and a generally nodular pattern. It is indolent, affects the trunk, head and neck, responds to radiotherapy and has an excellent prognosis.
- *Primary cutaneous marginal zone lymphomas* include those previously called primary immunocytomas or plasmacytomas. They generally have a diffuse pattern with negative Bcl-6 staining except in reactive germinal centres. They are Bcl-2 positive. Bcl-2 is an integral membrane protein located on endoplasmic reticulum, mitochondrial outer membranes and the nuclear envelope. It suppresses apoptosis by interfering with caspases. They are composed of predominantly lymphoid, lymphoplasmacytoid or plasma cells aggregating around blood vessels. They are radiosensitive and the prognosis is good.
- *Primary cutaneous diffuse large B cell lymphoma of the leg* (Fig. 12.59) associated with lymphoedema affects especially elderly males and appears to be a distinct variant, probably of follicular centre origin, with an intermediate prognosis. There are sheets of Bcl-2 positive centroblast cells.
- *Primary cutaneous diffuse large B cell lymphoma (other forms)* are usually secondary and include intravascular large B cell lymphoma and plasmablastic lymphomas.

Localized disease may be treated with surgical excision or radiotherapy. Systemic disease requires standard chemotherapy with adjuvant anti-CD20 antibody (Rituximab) and newer related antibodies.

Myeloid malignancies

Leukaemic deposits in the skin are uncommon except in *myelomonocytic leukaemia* (Fig. 12.60). Leukaemia usually presents in the skin as widespread purpura (Fig. 12.61). Myelodysplastic syndromes (MDS), a third of which progress to acute leukaemia, may present as *Sweet's syndrome* (Fig. 12.62), *vasculitis* or *pyoderma gangrenosum*. Other autoimmune phenomena (vitiligo, alopecia areata and eczema) are common in MDS. Generalized pruritus, infections of the skin consequent to immunosuppression and, very occasionally, erythroderma may be presenting features of leukaemia. Skin biopsy, a full blood count and bone marrow biopsy will help to establish the diagnosis.

Pseudolymphomas of the skin

The pseudolymphomas of the skin have the architectural and cytological features of a neoplastic proliferation of lymphoid tissue but pursue a benign course. They therefore mimic B or T cell lymphomas but are polytypic in immunophenotyping tests. There is also no dominant clonal population detected by the polymerase chain reaction. Confusion arises when a pseudolymphoma turns into a lymphoma, as may happen with *lymphomatoid papulosis*; it may be that in this variety there is a clonal proliferation when previous host control is lost. In some cases, the cause of the pseudolymphoma is known. For example, drugs, particularly anticonvulsants including carbamazepine and phenytoin, are responsible for a pseudolymphoma (usually T cell) of the skin often with erythroderma associated with fever, lymphadenopathy, eosinophilia, hepatosplenomegaly and disturbed liver function. This occurs particularly in individuals of African descent and resolves slowly with cessation of the drug. Arthropods may produce a pseudolymphomatous picture, for example nodular scabies and the persistent insect bite reaction. Borrelial

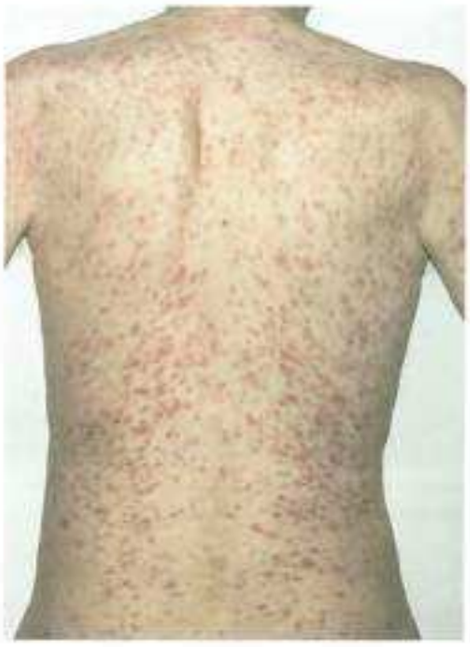


Fig. 12.60 Leukaemia cutis. Firm papules or nodules may occasionally occur in leukaemia, particularly myelomonocytic leukaemia (FAB classification M5B).

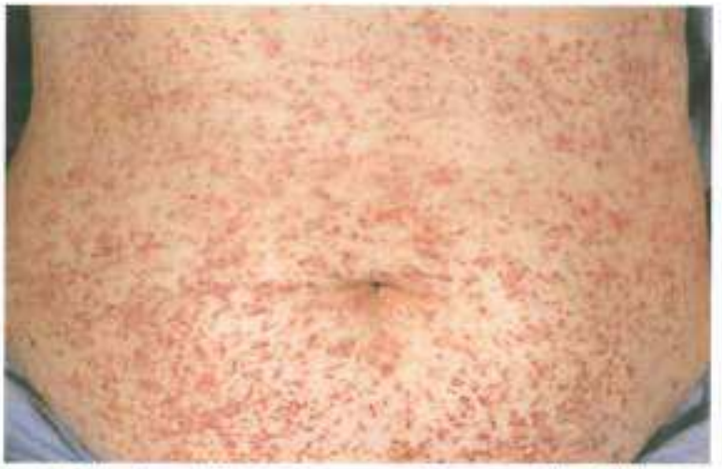


Fig. 12.61 Leukaemia. The most common cutaneous presentation of leukaemia is purpura.

infection may produce a B cell pseudolymphoma as may trauma from, for example, injections or an infection such as herpes zoster.

Actinic reticuloid (Ch. 18) is thought to represent a cutaneous T cell pseudolymphoma.

LYMPHOCYTOMA CUTIS

A distinct entity of unknown aetiology that presents as a cutaneous B cell pseudolymphoma.

Aetiology

The condition was first described by Kaposi as sarcomatosis cutis and subsequently as lymphocytoma cutis. Other names have included lymphadenosis maligna cutis, pseudolymphoma of Spiegler and Fendt and cutaneous lymphoid hyperplasia. The stimulation for the accumulation of lymphocytes in the skin is not known. It occurs in young adults.

Clinical Features

Symptoms

Asymptomatic persistent small lumps on the skin, usually the face.

Morphology

There are persistent flesh-coloured, purple or brown papules, plaques or nodules (Fig. 12.63).

Distribution

The most common variety is localized to the face, particularly over the nose, earlobes or cheeks. It may occur in a more generalized way on the chest and upper extremities.

Histopathology

The appearances are those of an overexuberant reactive B cell hyperplasia. The epidermis is uninvolved and a papillary dermal Grenz zone is usual. Occupying the dermis and often the subcutaneous fat is a dense nodular, polymorphic inflammatory cell infiltrate. Lymphoid follicles with germinal centre formation are characteristic. The cellular infiltrate consists of mature lymphocytes, plasma cells, eosinophils and occasional giant cells. The polymorphic nature of the infiltrate, accompanied by lymphoid follicle formation, characterizes this lesion.

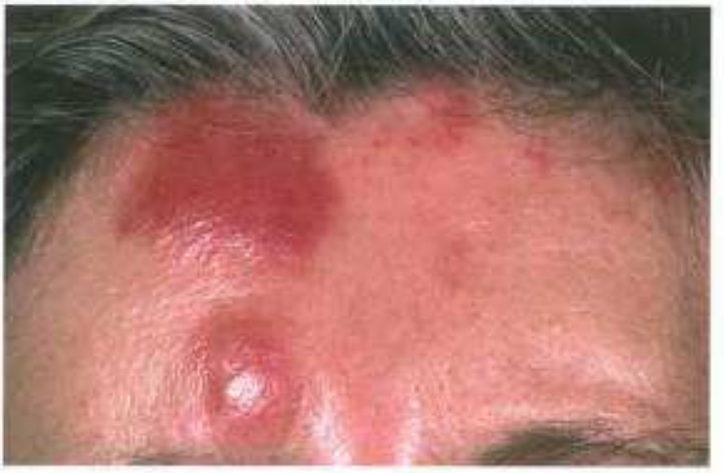


Fig. 12.62 Sweet's syndrome. Plum-coloured plaques are present. She was found to have acute myeloid leukaemia. (Courtesy of Dr A. C. Pembroke.)

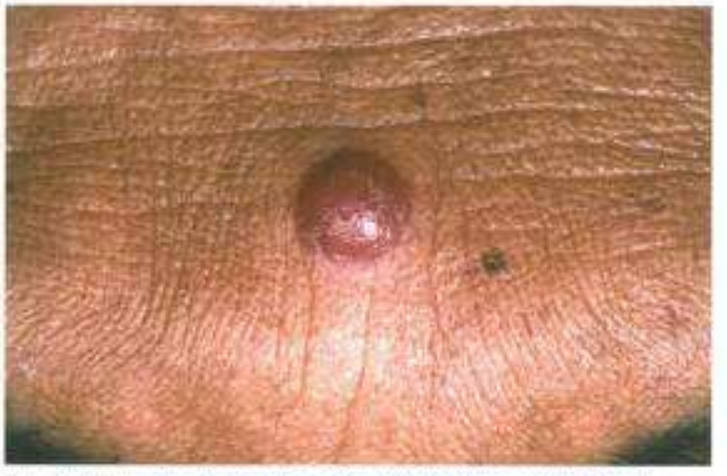


Fig. 12.63 Lymphocytoma cutis. A solitary nodule was present. The nose and forehead are common sites. The diagnosis is made histologically. Gene rearrangement studies are negative. It is radiosensitive. This lesion was excised without recurrence.

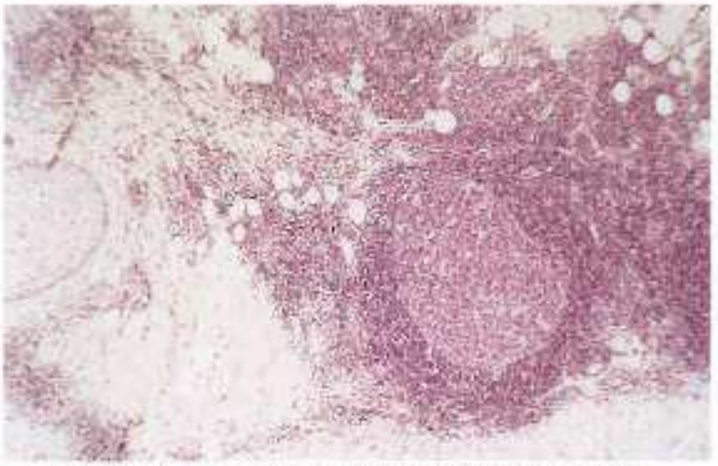


Fig. 12.64 Lymphocytoma cutis. A polymorphic infiltrate of lymphocytes, plasma cells and scattered eosinophils without primitive cell forms or mitoses is present in the dermis and often in the fat.

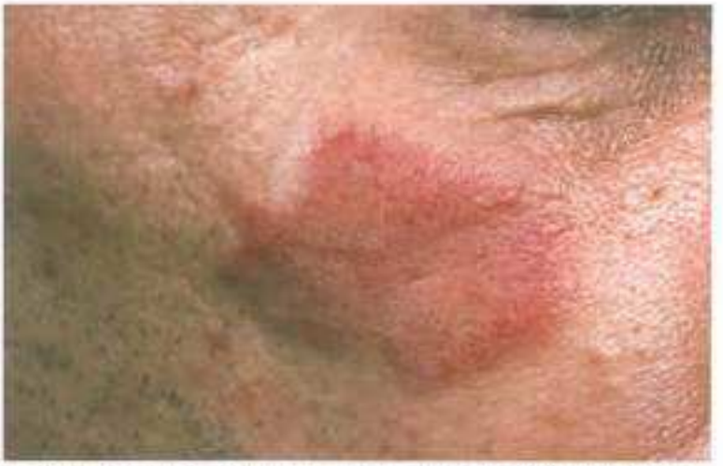


Fig. 12.65 Jessner's lymphocytic infiltrate of the skin. A diffuse red plaque without scaling is present on the cheek. A skin biopsy establishes the diagnosis.

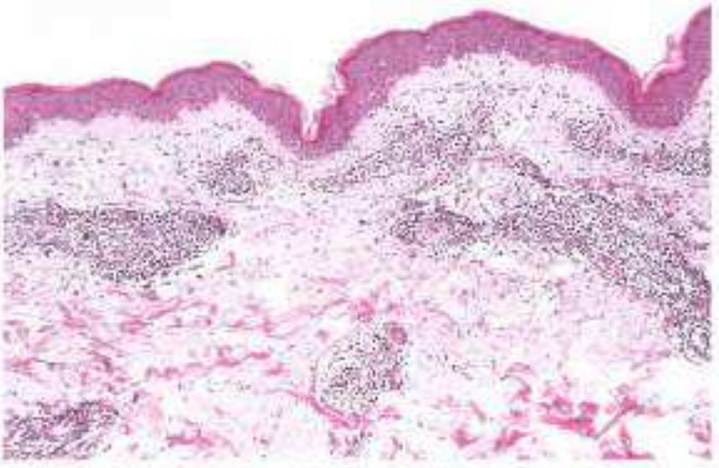


Fig. 12.66 Jessner's lymphocytic infiltrate of the skin. There are discrete collections of mononuclear cells around the blood vessels and sweat ducts.

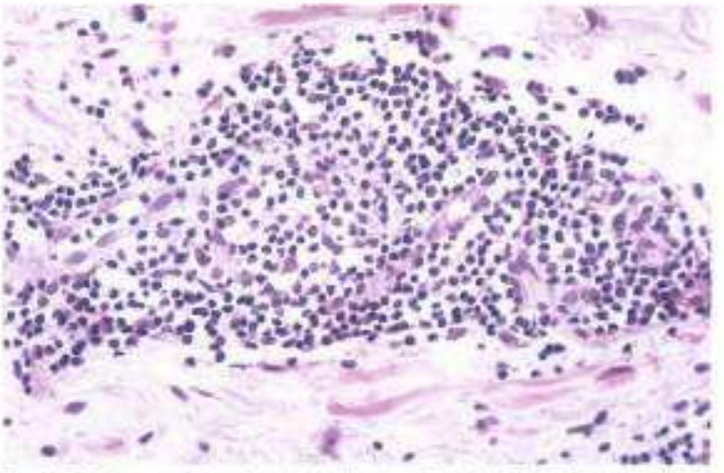


Fig. 12.67 Jessner's lymphocytic infiltrate of the skin. The infiltrate consists of uniform, mature lymphocytes.

Management

The diagnosis is made by biopsy (Fig. 12.64). The benign nature of the condition is confirmed by immunophenotyping and immunoglobulin and T cell gene rearrangement analysis to prove that it is not clonal. Solitary lesions may be excised. It also responds well to small doses of radiotherapy.

Benign lymphocytic infiltrations of the skin

JESSNER'S LYMPHOCYTIC INFILTRATE

A chronic benign T lymphocyte infiltration of the skin, occurring predominantly on the face and chest.

Aetiology

The cause is unknown. The majority of the lymphocytes are $CD4^+$ helper cells. It may be a variant of cutaneous lupus erythematosus.

Clinical Features

Symptoms

Asymptomatic disfiguring plaques on the chest and face (Fig. 12.65).

Morphology

There are multiple, purple or red-brown papules, nodules or plaques, which tend to come and go at random.

Distribution

The lesions occur particularly on the face but also on the trunk.

Histopathology

The epidermis is unaffected. Within the dermis is a monomorphic lymphocytic infiltrate (Figs 12.66 and 12.67) that surrounds blood vessels and sometimes cutaneous adnexae. It is thus indistinguishable from chronic lymphatic leukaemia. The absence of hyperkeratosis, epidermal atrophy and basal cell liquefactive degeneration distinguishes it from discoid lupus erythematosus and immunofluorescence is negative.

Management

Biopsy is necessary for diagnosis. The lymphocytic infiltrate is entirely benign as is the course of the condition. Treatment is unsatisfactory but

- **Superpotent topical steroids** are the first line of treatment.
- **Antimalarials** such as hydroxychloroquine and mepacrine are sometimes useful.
- **Superficial X-rays** can be considered.

Bacterial and spirochaetal infections | 13

If the integument is intact and the host is immunocompetent, it is difficult to infect the skin, even experimentally. The relative dryness of the skin, antibacterial substances in sebum and the resident microflora limit colonization of the skin by potential pathogens. The resident organisms include the anaerobic diphtheroid *Propionibacterium acnes*, aerobic diphtheroids, *Staphylococcus epidermidis*, a small number of anaerobic staphylococci and, in moist areas, Gram-negative bacilli. These only become pathogens if given the opportunity, for example around indwelling catheters or prosthetic valves, or in patients who are immunocompromised, either congenitally (e.g. chronic granulomatous disease or Job's syndrome) or acquired (from drugs or disease).

The majority of primary pyodermas are secondary to infection with *Staphylococcus aureus* or group A streptococci. Staphylococci are not part of the normal skin flora but may colonize the skin either transiently or more permanently in certain sites such as the nose, axillae, groin and perineum. They are common invaders of eczematous, traumatized or immunocompromised skin and are responsible for impetigo, folliculitis, and surgical wound infections and may produce toxins. These include toxic shock syndrome, enterotoxins, Panton Valentine Leucocidin (PVL) and exfoliative toxins (staphylococcal scalded skin syndrome). Staphylococci are easily transferred from carrier sites via the hands and this is important in hospitals and nurseries. Host factors, especially immunosuppression and topical and systemic steroids, increase susceptibility to infection. Neonates have a minimal protective cutaneous flora and are especially vulnerable. The widespread emergence of staphylococcal resistance to antibiotics including methicillin has become a major problem in therapy. Hospital acquired methicillin resistant *Staphylococcus aureus* (MRSA) is multidrug resistant and causes major systemic toxicity. Community acquired MRSA affects children and young adults (and often those involved in close contact sports). It can cause serious infections including osteomyelitis, septic arthritis, necrotizing pneumonitis, necrotizing fasciitis, orbital cellulitis, endocarditis and brain abscesses. It is usually non-β lactam antibiotic sensitive and responds to clindamycin, doxycycline, minocycline, rifampicin, septrin, teicoplastin and vancomycin. It does contain the staphylococcal cassette chromosome (SCC) *mec* type IV gene and carries a highly virulent PVL gene, which is associated with skin necrosis, furunculosis and lung infections. PVL is a cytotoxic protein produced by *S. aureus*, which exhibits a highly specific lytic activity against polymorphonuclear cells, monocytes and macrophages.

Essentially, all group A streptococci are haemolytic and can be identified in the laboratory by their sensitivity to bacitracin. *Streptococcus pyogenes* (a group A streptococcus) does not usually colonize normal skin because skin surface lipids, especially free fatty acids, inhibit its growth. Colonization and infection generally require a disruption in the integrity of the epidermis and result in primary pyodermas, such as impetigo and folliculitis, and in cellulitis, including perianal cellulitis, erysipelas and blistering distal dactylitis. Strains of pharyngeal group A streptococci may also produce erythemagenic toxins, which result in scarlet fever or, more commonly, a milder variant and toxic erythema that causes a widespread desquamation, particularly of the extremities. Severe infections with Lancefield group A streptococci (e.g. puerperal sepsis, scarlet fever and bacteraemia) and non-suppurative allergic sequelae (e.g. acute rheumatic fever, acute glomerulonephritis and erythema nodosum) are rare in the West. This is probably because of improved living standards (infection increases with heat, humidity, poor hygiene and overcrowding), antibiotic therapy and reduced virulence of the organisms. However, there has been a resurgence of more serious infections including a streptococcal toxic shock syndrome, necrotizing fasciitis and bacteraemia. This may be a result of the re-emergence of more virulent strains, which often possess anti-phagocytic M proteins, pyrogenic strains (leading to bacteraemia and invasion) and a decrease in the herd immunity. Toxin-mediated streptococcal or staphylococcal disease may be responsible for Kawasaki disease and precipitate guttate psoriasis.

Group B streptococci colonize mucous membranes but not the skin. The organism is sexually transmitted in adults and colonizes the vagina, male urethra, throat and rectum.

Coryneform bacteria are Gram-positive rod-shaped organisms, known as diphtheroids. Aerobic coryneforms are responsible for erythrasma and trichomycosis axillaris. Anaerobic coryneforms are part of the resident flora and play an important role in acne.

Pseudomonas aeruginosa (*Pseudomonas pyocyanea*) is an aerobic Gram-negative rod bacillus. It is a transient colonizer of the axillae, external ear and anogenital region but is usually kept in check by the dominant Gram-positive cocci population on the skin. It is present in soil, water and in the gastrointestinal tract (regularly in infants, occasionally in adults).

The other bacterial infections included in this chapter affect the skin secondarily, but the cutaneous signs assume importance for they may indicate the cause of a systemic disturbance. Those included are tuberculosis, gonococcaemia, meningococcaemia and syphilis. Spirochaetes are long, thin-walled, flexible, spiral organisms. They have some features in common with bacteria but are unusual in that their mobility is achieved with an internal axial filament rather than the external flagella used by other mobile bacteria. There are three genera, *Treponema*, *Borrelia* and *Leptospira*. *Treponemum pallidum* causes syphilis, *T. pallidum* subspecies *pertenue* causes yaws and *T. carateum* causes pinta. *Borrelia burgdorferi* is a spirochaete transmitted to humans by tick bites and causes Lyme disease. The *Leptospira interrogans* complex causes leptospirosis and Weil's disease.

Impetigo

An acute, contagious and superficial infection of the skin caused either by *S. aureus* or a β-haemolytic streptococcus, or both.

Aetiology

Impetigo is common in the young. Outbreaks occur in institutions such as nurseries and boarding schools. Sometimes it follows insect bites, head lice or trauma. The skin is more vulnerable to secondary bacterial infection in eczema, when it may be described as being 'impetiginized'.

Clinical Features

Symptoms

The patient or parent often remark that the lesions start as blisters.

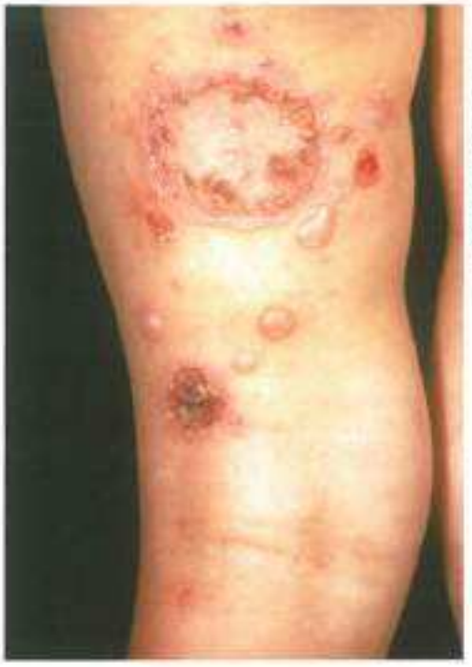


Fig. 13.1 Bullous impetigo. There are many purulent blisters of various sizes, some of which have dried forming yellow crusts, especially at their margins. *S. aureus* produces an exfoliative toxin which binds to desmoglein 1 and leads to acantholysis within the granular cell layer.

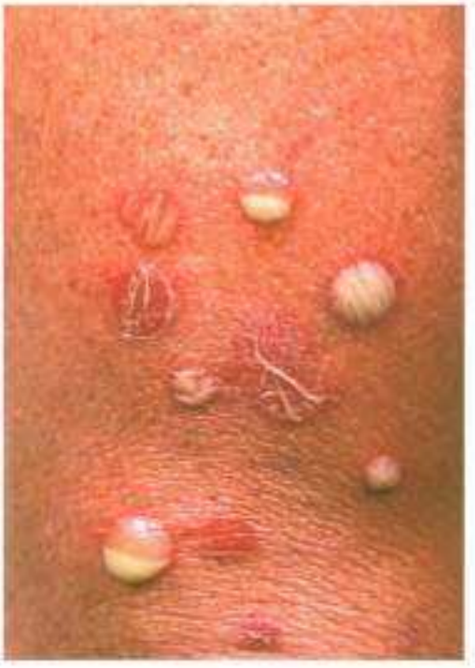


Fig. 13.2 Bullous impetigo. The fluid levels made by the purulent material are clearly visible. Other blisters have become more flaccid. It occurs in intact skin and is considered to be a localized form of the staphylococcal scalded skin syndrome.

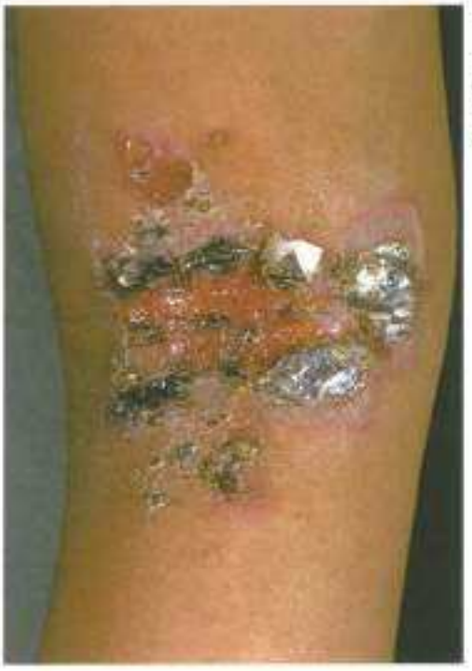


Fig. 13.3 Impetigo. The lesions start as blisters that contain pus and subsequently become eroded and crusted.

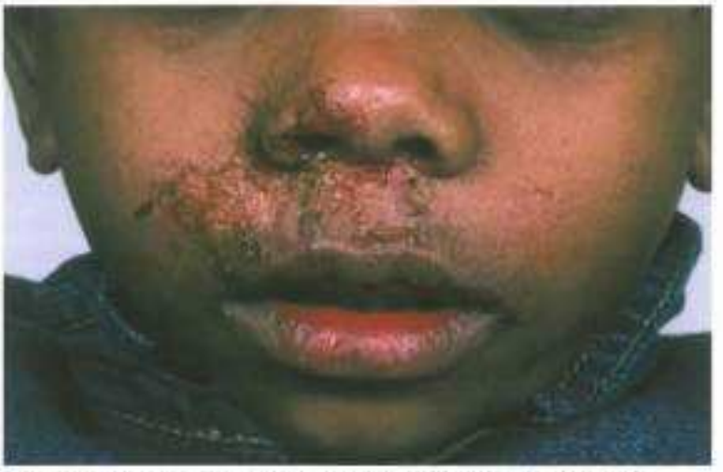


Fig. 13.4 Impetigo. The face is a common site. Golden crusts are present. Infants and children are particularly at risk.

Morphology

The blisters (Fig. 13.1) remain for a couple of days. Yellow pus is often clearly visible (Fig. 13.2). Subsequently they rupture (Fig. 13.3) and the purulent exudate dries to form golden-coloured crusts (Fig. 13.4). Sometimes the blisters are transient and the crusts are the most apparent feature (Fig. 13.5), although remnants of the blistering process may be seen at the margin.

Distribution

Impetigo occurs anywhere, especially the face.

Systemic

Nephritis may occur 3 weeks after infection with the nephritogenic strain of streptococcus but it is becoming uncommon as socioeconomic conditions improve.

Management

The condition spreads rapidly. If the infection occurs more deeply, a shallow ulcer is present under the crust. This is more common in the tropics and is often seen on the lower limbs secondary to insect bites (Fig. 13.6). It presented particular problems to American troops in Vietnam. The condition is known as *ecthyma* (Fig. 13.7). Other blistering disorders such as acute eczema or herpes simplex (Fig. 13.8) (particularly primary) may become impetiginized. Bullous tinea (especially caused by *Trichophyton tonsurans*) is occasionally mistaken for impetigo. Treatment includes:

- topical antibiotics, for example fucidin or mupirocin ointment
- systemic antibiotics for 5 days; they are effective within 24 hours: streptococci respond to penicillin or erythromycin, but many staphylococcal strains are resistant and flucloxacillin is the preferred drug. A swab for culture and antibiotic sensitivity is useful for MRSA-induced impetigo.

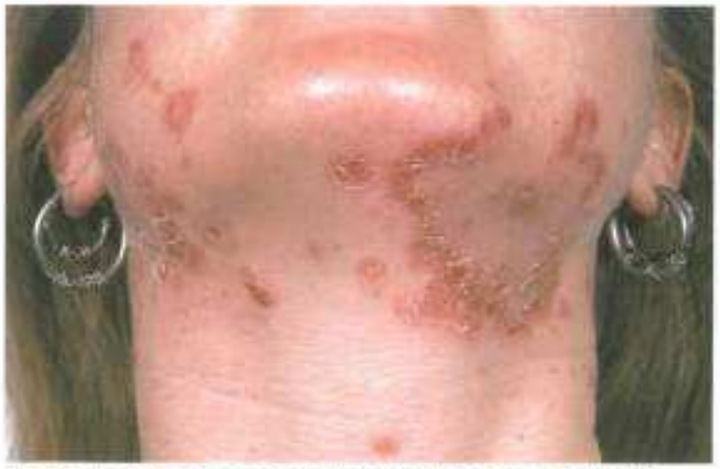


Fig. 13.5 Impetigo. The crusts are often arranged in an annular fashion. The lesions spread quickly, and systemic rather than topical antibiotics are usually necessary.

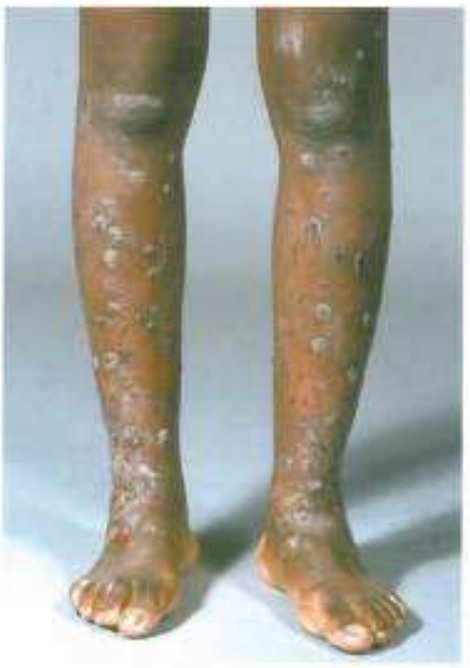


Fig. 13.6 Ecthyma. Crusted and eroded lesions are present mainly on the lower legs. Insect bites are often responsible for the sepsis. (Courtesy of St Mary's Hospital.)

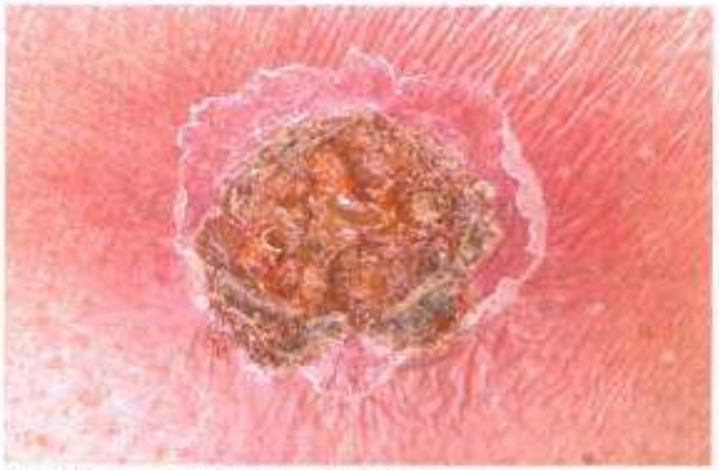


Fig. 13.7 Ecthyma. The lesion is painful and has a yellow crust that surmounts a shallow ulcer. There is surrounding inflammation.

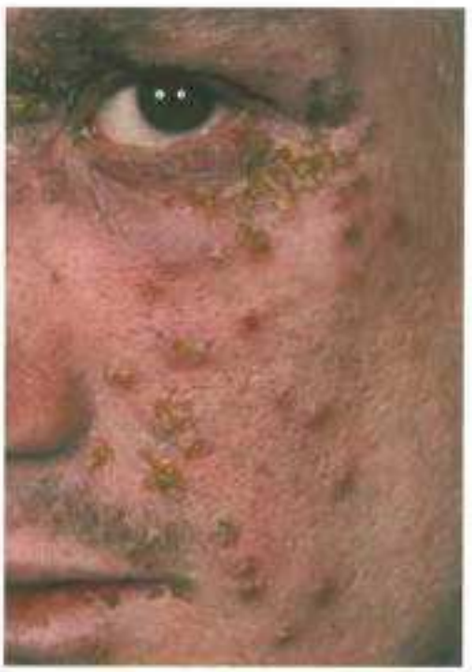


Fig. 13.8 Impetiginized eczema herpeticum. These vesicles here became impetiginized (secondarily infected with, usually, *S. aureus*), but the prime pathology is herpes simplex in a patient with atopic eczema.

Staphylococcal scalded skin syndrome

A blistering condition occurring throughout the granular cell layer without necrosis or inflammation, resulting in denudation of the skin. It usually occurs in young children.

Aetiology

This is an uncommon condition of infants and children under the age of 5 years. It is caused by an epidermolytic toxin, usually produced by group 2 staphylococci phage type 71 or 55 from the nasopharynx or conjunctivae. Exfoliative toxins A and B are implicated and probably cause splitting between the desmosomes in the granular cell layer by directly binding to desmoglein 1. It appears to be an idiosyncratic response since other members of the family only develop impetigo. It is also seen in children deficient in immunoglobulins or in immunocompromised adults where there is systemic absorption of large quantities of the toxin. *Bullous impetigo* is a localized form of the staphylococcal scalded skin syndrome, with superficial flaccid bullae caused by the exfoliation, which leaves behind a raw area of denuded skin. Probably an appropriate antibody response to the exfoliating toxin results in bullous impetigo and an inadequate human immune response predisposes to the staphylococcal scalded skin syndrome. Lyell was the first to describe the scalded skin syndrome although, in retrospect, only one of his original four patients had a staphylococcal infection. (The others had toxic epidermal necrolysis where there is also a mucositis.) The histopathology shows a superficial blistering in the granular cell layer.

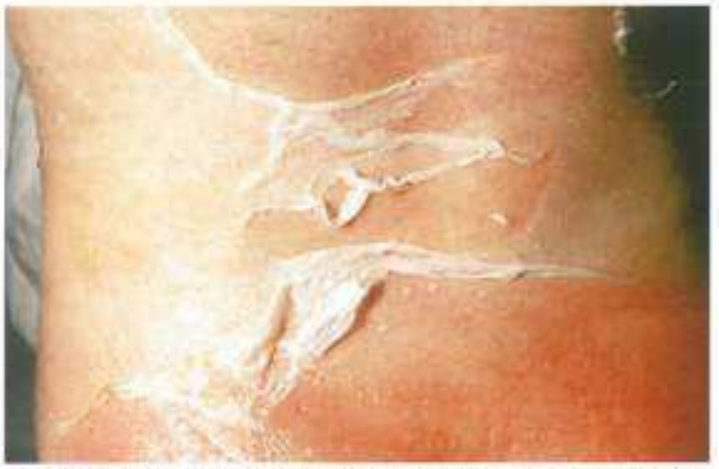


Fig. 13.9 Staphylococcal scalded skin syndrome (Lyell's disease). The skin is red, raw and desquamates in sheets. (Courtesy of St Bartholomew's Hospital.)

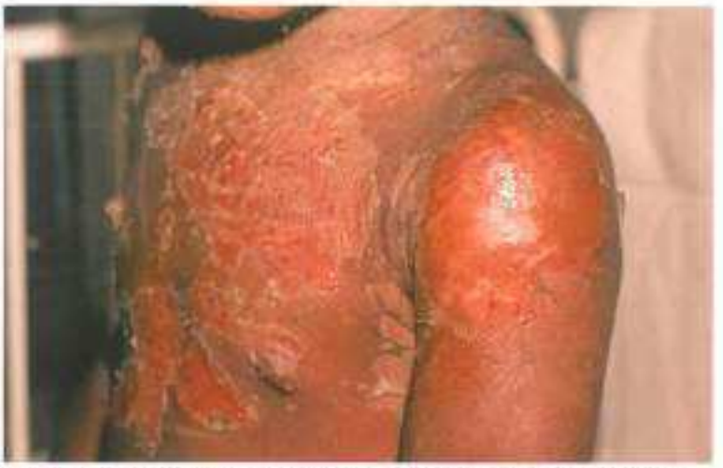


Fig. 13.10 Staphylococcal scalded skin syndrome. The skin is tender, raw, denuded and eroded on the shoulder and torso. The lesions heal rapidly with the appropriate antibiotics.

Clinical Features

Symptoms

The child is ill, irritable, crying and feverish. The skin burns and is tender to touch.

Morphology

The burning is followed by erythema, superficial blistering and widespread desquamation of the epidermis in sheets (Fig. 13.9), resulting in red, raw erosions (Fig. 13.10). The Nikolsky sign is positive.

Distribution

Most or all of the body is involved and especially areas of friction and around body orifices, including the lips but not the mouth, where desmoglein 1 is absent.

Management

Early recognition, swabs for microbiology and treatment with appropriate intravenous penicillins, fluid and electrolyte management are life saving. The mortality is low in children but high in immunocompromised adults.

Septic folliculitis (Bockhart's impetigo)

An acute painful, pustular eruption of hair follicles caused by *S. aureus streptococci* and other bacteria.

Aetiology

The folliculitis affects the outermost part of the hair follicle canal. It is common in patients being treated with potent topical steroids, particularly under polythene occlusion. It may occur secondary to contaminated oils or waxes.

Superficial folliculitis is usually caused by *S. aureus* but occasionally by *S. pyogenes*. Deeper infections of the hair follicle result in furunculosis or carbuncles. Other microbiological causes include *Ps. aeruginosa*, *Pityrosporum* yeasts, Gram-negative organisms (in rare cases of acne treated with antibiotics) and HIV, which causes an itchy eosinophilic folliculitis. These and pseudofolliculitis, where organisms are not found, are dealt with elsewhere.

Sycosis barbae is a chronic deep-seated staphylococcal infection of the beard area. It is only seen in men (Fig. 13.11) and is now very rare in Western societies, probably as a result of better hygienic conditions and the widespread availability and early use of antibiotics.

Clinical Features

Symptoms

Painful spots on the limbs.

Morphology

Small, tender, distinct, yellow pustules (Fig. 13.12) surrounded by erythema are present. A hair is usually discernible in the centre of each pustule.

Distribution

The lesions occur most commonly on the limbs in the hirsute.

Management

It is important to take swabs for cultures and sensitivities. They will be negative in pseudofolliculitis. Carrier sites should be swabbed in recurrent folliculitis. Erythromycin or flucloxacillin are the antibiotics of choice. Mupirocin may be helpful topically. Rifampicin 300 mg b.d. combined with clindamycin 150 mg b.d. for 10 weeks may be helpful in folliculitis of the scalp in black races (Chapter 26).

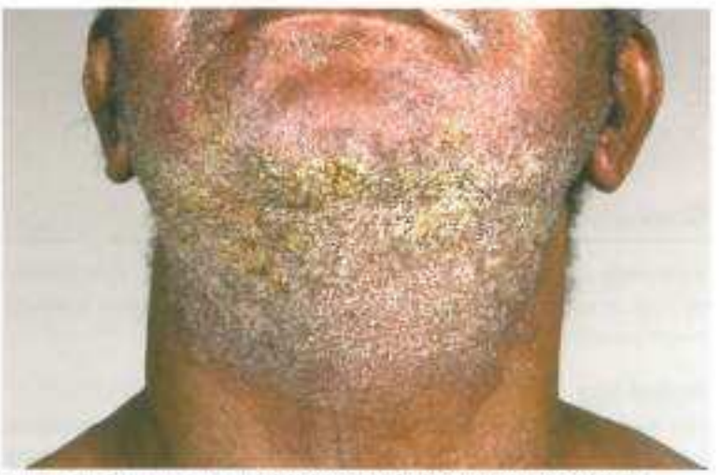


Fig. 13.11 Sycosis barbae. Staphylococcal infection of the beard area is uncommon in Western societies, probably because of improved hygiene and early use of antibiotics.

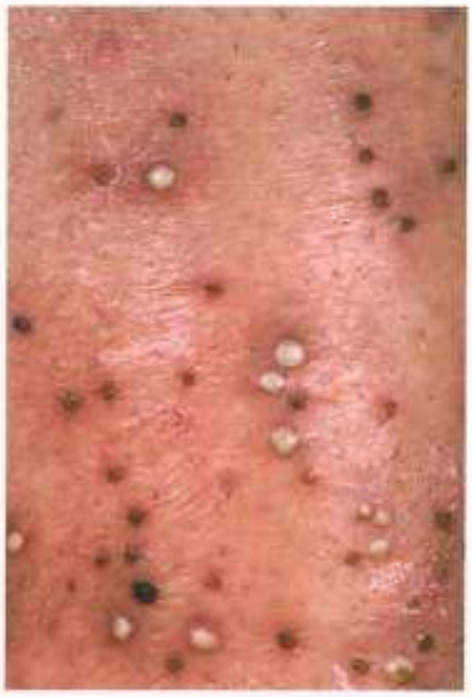


Fig. 13.12 Septic folliculitis. The pustules are yellow and the lesions painful. A swab for microbiology will reveal the responsible organism.

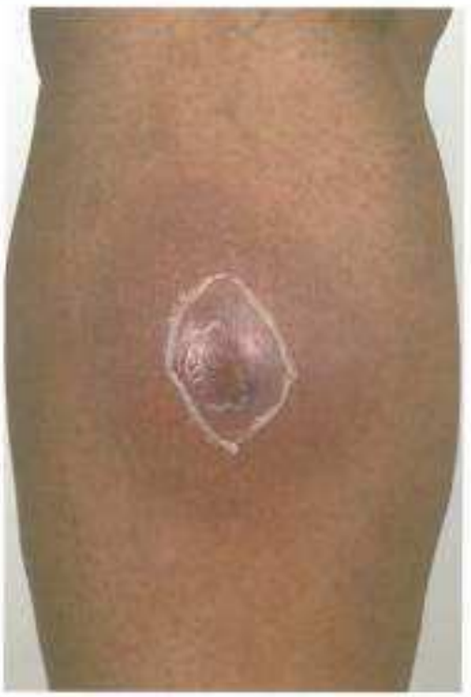


Fig. 13.13 Furunculosis. A large boil is present. It is tender, swollen and inflamed. There is desquamation over the surface. It is about to discharge.

Furunculosis

An acute deep abscess of the hair follicles usually caused by *S. aureus*.

Aetiology

Furunculosis differs from folliculitis in that the entire follicle is involved and there is a greater degree of inflammation, which spreads away from the hair follicle into the surrounding dermis. The condition is caused by *S. aureus*, which is usually also present in the nose, axillae or perineum. It is most common in adolescents and young adults, and the patient is invariably otherwise healthy. A search for diabetes mellitus, although always quoted in textbooks, is commonly fruitless, but it may represent an early sign of immunosuppression. Potent topical steroids may cause septic folliculitis.

Clinical Features

Symptoms

An acute painful swelling that may discharge pus.

Morphology

It may present as a boil or carbuncle. A boil is a red, painful nodule containing pus (Fig. 13.13), which discharges spontaneously (Fig. 13.14) and heals with or without scarring (depending on the depth of the lesion). This process takes several days. Several lesions may be present (Fig. 13.15) especially in recurrent cases. A *carbuncle* is an infection of contiguous hair follicles that begins as a nodule and enlarges to produce an inflamed mass which discharges pus from multiple follicular orifices. A carbuncle is, therefore, a collection of boils. The patient may be quite unwell, with a fever.

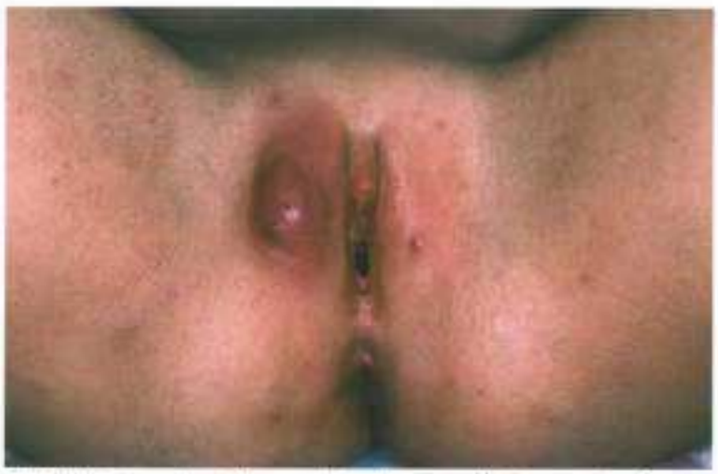


Fig. 13.14 Furunculosis. Many patients with recurrent boils are carriers of *Staphylococcus aureus* in the anterior nares, axillae, groin and/or perineum. They usually do not have lesions in these areas, unlike here.

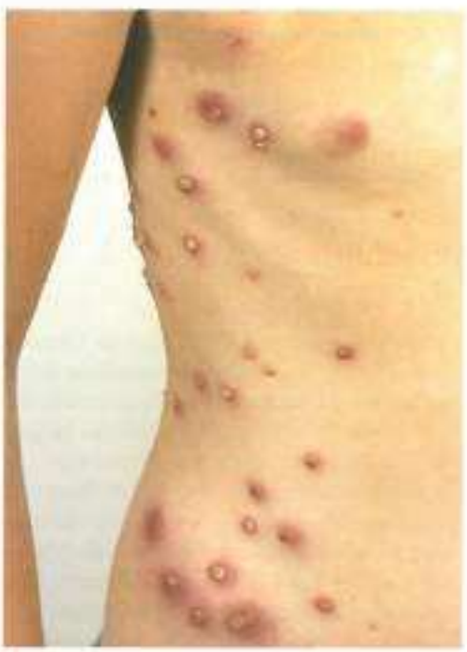


Fig. 13.15 Furunculosis. Painful red nodules are present in various stages of development. Patients who develop recurrent boils are usually staphylococcal carriers.

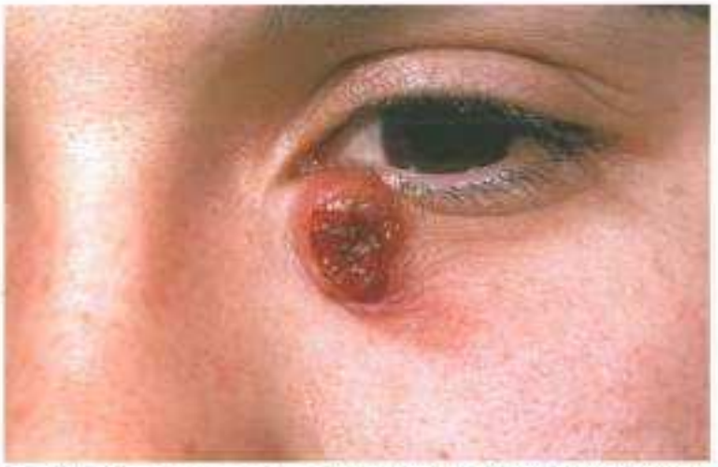


Fig. 13.16 Chancriform pyoderma. The lesion lasts a few weeks and, although thought to be staphylococcal, does not respond very well to antibiotics. (Courtesy of Dr Dorothy Vollum.)

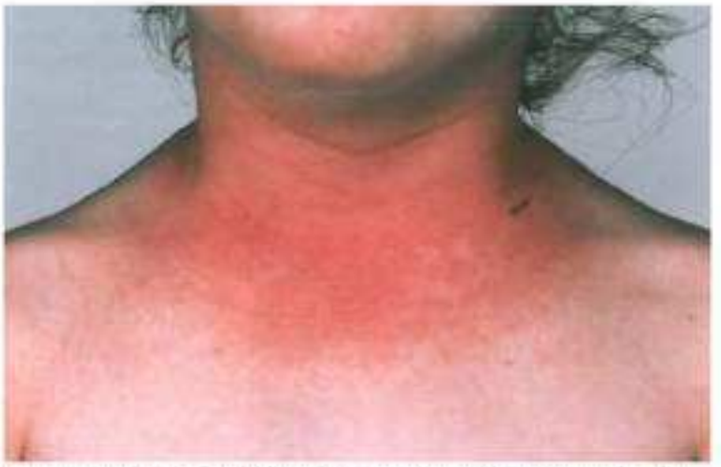


Fig. 13.17 Scarlatina. There is a diffuse eruption of scarlet macules. It starts on the face and neck following a high fever, sore throat, headache and vomiting.

Distribution

Boils and carbuncles may occur anywhere. A *stye* (hordeolum) is a staphylococcal infection of the eyelash and represents a small boil.

Chancriform pyoderma is of uncertain aetiology but probably is a reaction to a staphylococcal infection induced by trauma. It is an indolent well-defined ulcer with a red margin. It occurs around the eye (Fig. 13.16) or mouth.

Management

If the boil is pointing, the pus may be drained. A swab should be taken for culture. Erythromycin or flucloxacillin are usually effective, but therapy must be changed if the sensitivities indicate resistance. Rifampicin 300 mg twice daily combined with cefalexin 500 mg twice daily may then be required.

Occasionally, an otherwise healthy patient suffers from *recurrent boils*. Swabs should be taken from the carrier sites (nose, axillae, scalp, groin and perineum), one or more of which are almost always positive. Topical mupirocin twice daily for 7 days is appropriate since it has no systemic use and, therefore, there are no fears regarding resistance. It is useful to add hexachlorophane to the bath. If swabs from carrier sites are negative, then the whole household should be swabbed to determine the source of the staphylococci. Cases do occur where the spouse may be the source of the infection and treatment of the spouse ends the recurrences. Rifampicin is also reported as being effective in eradicating *S. aureus* in persistent nasal carriers.

Scarlet fever (Scarlatina)

A streptococcal infection resulting in high fever, vomiting and a characteristic exanthem and enanthem.

Aetiology

Scarlet fever is caused by a group A β-haemolytic streptococcus that produces an erythemagenic toxin. Infection is spread by fomites from either an infected patient or an asymptomatic carrier. It is usually present in the tonsils and pharynx but can arise from the skin and from infected surgical wounds (surgical scarlet fever). It was often fatal in the preantibiotic era, but the morbidity, mortality and non-suppurative sequelae of rheumatic fever and glomerulonephritis are much less serious now, not only because of antibiotics but also because the erythemagenic toxin is more likely to be streptococcal pyrogenic exotoxins (SPE) B and C rather than the more virulent SPE-A toxin, which was prevalent at the beginning of the 20th century. It occurs in children but is rare in infants because it requires previous exposure to generate an antitoxin antibody and a delayed hypersensitivity response. Uncommon complications are pneumonia, pericarditis, meningitis, hepatitis, glomerulonephritis and rheumatic fever.

Clinical Features

Symptoms

After an incubation period of 1–4 days, there is a sudden onset of high fever, vomiting, headache, sore throat and sometimes severe abdominal pain, followed by a rash within 12–48 hours.

Morphology

Exanthem There are scarlet macules on a background of diffuse erythema (Figs 13.17 and 13.18) (most marked in the axillae and groins), which become punctate and rough on the limbs. Linear petechial streaks (Pastia's lines) occur in the flexures (axillae, groin and elbow). There is circumoral pallor. It resolves with desquamation, which is most pronounced on the palms (Fig. 13.19), soles and lips, and clears within 7 days.

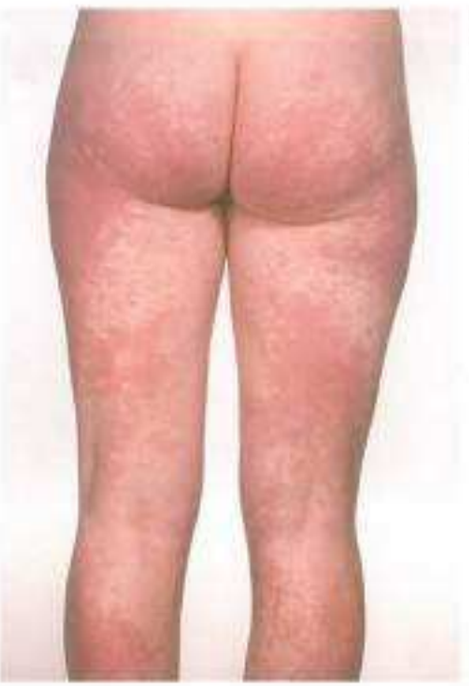


Fig. 13.18 Scarlatina. There is a diffuse erythema of the limbs. The patient was febrile and the antistreptolysin titre was significantly raised.

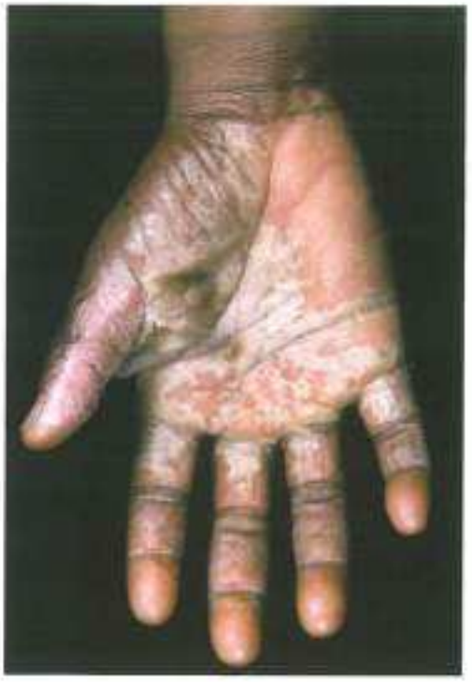


Fig. 13.19 Scarlatina. Erythema and peeling of the palmar skin were secondary to a streptococcal infection. Desquamation of the lips is also usually present.

Enanthem The pharynx and tonsils are a beefy red colour and may have an exudate. Petechiae may occur on the palate. The tongue exhibits a characteristic change: initially it is coated white; as the reddened papillae project through, it looks rather like a 'white strawberry' and as all the white coating disappears, it resembles a red strawberry.

Distribution
It begins on the face and neck and spreads to the chest, axillae, abdomen and extremities.

Management
The white count is raised with a pronounced neutrophilia. Eosinophilia is common in the second week. Throat cultures are positive for group A β-haemolytic streptococci. Blood cultures are sometimes positive. Treatment is with phenoxymethylpenicillin (penicillin V), 250 mg four times daily for 10 days, or, if necessary, benzylpenicillin, 1.2 million units intramuscularly. Erythromycin, 250 mg four times daily, may be used for allergic patients. Cephalosporins, flucloxacillin and rifampicin are all also effective. Recurrences do occur in a minority of patients.

Blistering distal dactylitis

A streptococcal infection of the palms or distal phalanges sometimes with an upper respiratory tract infection.

Aetiology
Group A streptococci are almost always involved but occasionally group B organisms may be isolated. Children or teenagers are susceptible.

Clinical Features
Symptoms
A blister occurs on the finger (Fig. 13.20) or palm.

Morphology
The large blister contains seropurulent fluid.

Distribution
Palm or a finger, from whence it may extend onto the nailfold.

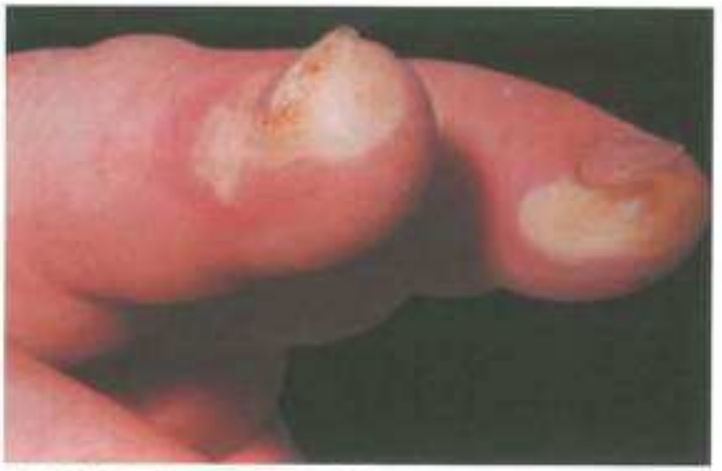


Fig. 13.20 Blistering distal dactylitis. There is blistering containing seropurulent fluid along the finger. It responds to penicillin. (Courtesy of Dr Lucia Martin-Moreno.)

Management
The organism is cultured from the blister fluid and is responsive to the appropriate antibacterial therapy.

Erysipelas and cellulitis

These are acute infections of the dermis and subcutaneous tissues caused by *S. pyogenes* and, occasionally, other organisms; they may result in profound systemic disturbances.

Aetiology
The distinction between erysipelas and cellulitis is often not clear clinically, but the teaching is that erysipelas is superficial, as it involves the dermis and upper subcutaneous tissue, whereas cellulitis may involve the entire subcutaneous tissue. The margins of erysipelas are much more clearly demarcated (Fig. 13.21) than those of cellulitis, and lymphangiitis is prominent. Erysipelas is almost always caused by group A β-haemolytic

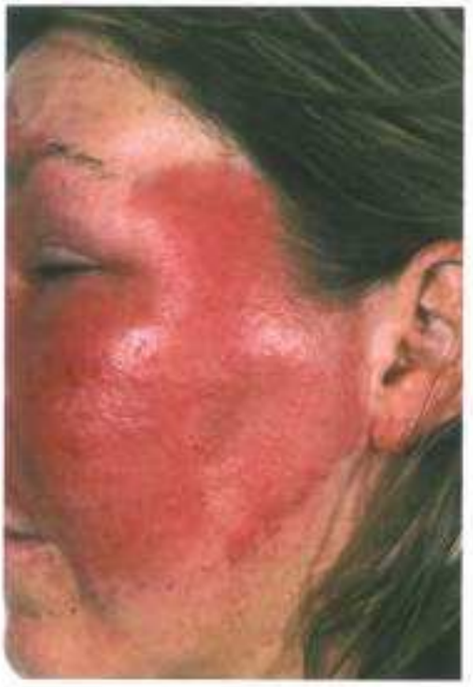


Fig. 13.21 Erysipelas. There is unilateral well-defined erythema and oedema of the face. The patient is frequently quite ill, has a high fever with rigors and may become confused.

streptococci. Cellulitis is usually caused by *S. pyogenes* but *S. aureus* or *Haemophilus influenzae* (becoming less common following vaccination against HIB) are occasionally responsible.

The disorder may occur at any age, and the undernourished, alcoholics and those with haematological malignancies, diabetes, HIV and nephritic syndrome are most prone. In clinical practice, however, the patient is often otherwise well but may endure recurrent attacks on the face or lower limbs. These are thought to be a consequence of lymphatic deficiency, possibly a pre-existing hypoplasia, that does not manifest itself until later on in life; it is aggravated by the infection and tends to recur. The point of entry may be a minor abrasion, otitis externa, tinea between the toes or following surgery (Fig. 13.22). Often there is no obvious cause. Cellulitis and erysipelas may spread via the lymphatics, causing lymphangiitis and suppurative lymphadenitis, and via the bloodstream, producing bacteraemia.

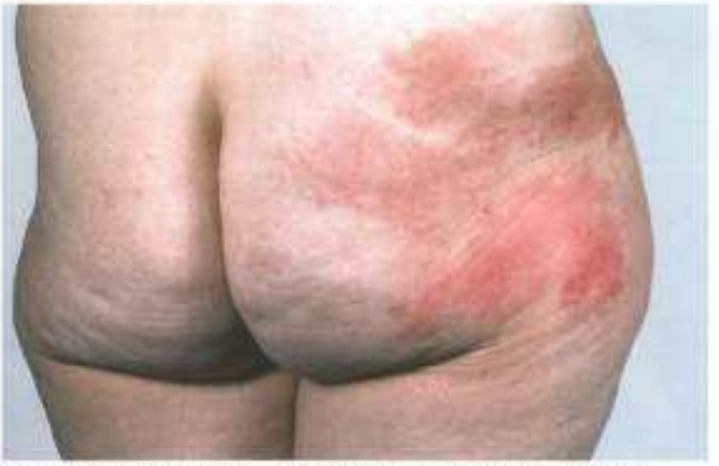


Fig. 13.22 Surgical cellulitis. This patient developed recurrent attacks of cellulitis after an inguinal lymph node biopsy.

Clinical Features

Symptoms

The onset is abrupt. The patient becomes ill, has a high fever with rigors and may vomit and become confused and occasionally delirious.

Morphology

Examination reveals a tender unilateral (occasionally bilateral) erythema (Fig. 13.23) and oedema, which sometimes blisters and becomes eroded.

Distribution

The face or leg (which may be left persistently oedematous).

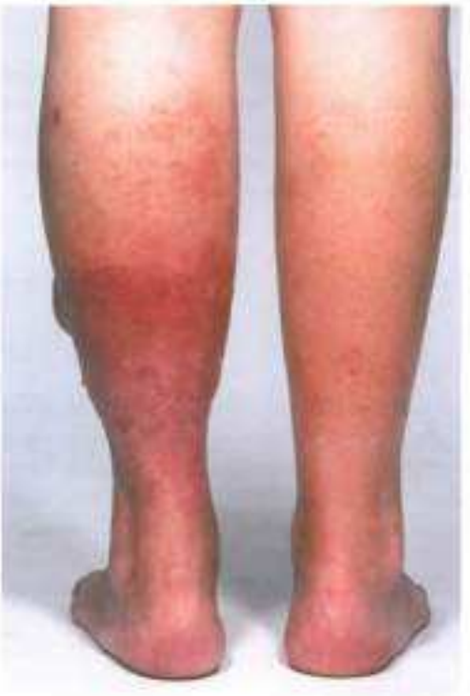


Fig. 13.23 Erysipelas. There is unilateral erythema, oedema and blistering of the leg. Patients may subsequently have recurrent episodes. Long-term low-dose penicillin or erythromycin may prevent them.

Management

This is a medical emergency as nephritis and septicaemia may follow.

Swabs are usually negative but the condition responds dramatically to penicillin, erythromycin or amoxycillin. Some patients, however, develop recurrent attacks, which can be prevented by a very small (250 mg) daily dose of phenoxymethylpenicillin or erythromycin for the rest of their lives, a fact that is often not well appreciated. The rationale for this treatment is not understood.

It is important to treat the portal of entry of the organism if it is detectable, e.g. tinea pedis, with antifungal agents.

Toxic shock syndrome

Toxic shock syndrome comprises fever, rash, desquamation, hypotension and multiple organ involvement; it was originally described as a staphylococcal toxic syndrome mediated by superantigens but it is now more commonly associated with toxin-producing group A streptococci.

Aetiology

The condition was first described in association with superabsorbent tampon use. Staphylococcal toxic shock syndrome toxin-1 (TSST-1) acts as a superantigen leading to the massive release of tumour necrosis factor-alpha (TNF-α) and interleukin 1 (IL-1) in particular. It has also been described, although much less commonly, in a non-menstrual context usually postoperatively or postpartum but also in association with burns, cellulitis, intravenous drug administration and HIV. Half of these instances are caused by TSST-1 but the rest are caused by staphylococcal enterotoxins. The condition is rarely reported nowadays since the reduction in use of superabsorbent tampons.

Streptococcal toxic shock syndrome was first reported in the late 1980s and is caused by a group A streptococcus possessing one of the antiphagocytic M proteins such as M1 or M3. These synthesize streptococcal pyrogenic exotoxins (SPEs), which were formerly known as scarlet fever or erythemagenic toxins. They either have a direct cytotoxic effect or act via the superantigen release system. Though there is a similar clinical appearance to staphylococcal toxic shock syndrome, skin is often the portal of entry (which is unusual in the staphylococcal syndrome) and there is frequently soft tissue infection (necrotizing fasciitis) or a localized bullous or haemorrhagic cellulitis. The condition occurs in young, otherwise healthy adults, and since toxic shock epidemics do not occur, it is probable that these individuals either lack immunity or have the receptors (HLA class II antigen on the antigen-presenting cell or Vb regions on the helper T cells) permitting activation by superantigens.

Clinical Features

Symptoms

The patient is ill with a fever, rash, hypotension and multiple organ involvement.

Morphology

There is a diffuse macular erythroderma or scarlatiniform eruption, with flexural accentuation and erythema and oedema of the palms and soles; desquamation, particularly acrally, follows 1–2 weeks later. There is a hyperaemia of the conjunctiva and mucous membranes.

Distribution

The eruption is generalized but often with flexural accentuation and particular involvement of the palms and soles. There is associated soft tissue infection. There may be a localized painful area with erythema and oedema; it can progress possibly to necrosis and gangrene.

Management

There is an appreciable mortality and since the syndrome progresses with dramatic speed to hypotension and organ failure, life-supportive measures should be instituted immediately. Penicillinase-resistant antibiotics are appropriate for staphylococcal infections and penicillin and clindamycin for streptococcal infection. There is no treatment that can neutralize the toxins or host cytokines at present but intravenous gammaglobulin has been advocated for overwhelming infections.

A possible variant of toxic shock syndrome caused by similar bacteria, although more commonly staphylococcal rather than streptococcal, is the *recalcitrant erythematous desquamating disorder* described exclusively in the acquired immunodeficiency syndrome (AIDS). It appears to be a toxin-mediated illness and is associated with fever and hypotension. There is a similar diffuse macular erythema leading to desquamation with oral and ocular injection and a strawberry tongue; the AIDS-related form differs in that it is a prolonged illness lasting many weeks, with frequent recurrences but with less organ involvement than in toxic shock syndrome and with significant mortality because of the underlying disease. The condition is sometimes known as *Red disorder*.

There is also a toxin-mediated erythema occurring around the perineum as a striking diffuse macular erythema 24 to 48 hours after a bacterial pharyngitis caused by toxin-producing staphylococci or streptococci. Here, there are also oral mucosal changes, including a strawberry tongue and erythema, oedema and convalescent desquamation of the palms and soles. There are no systemic effects but the patient may have diarrhoea. Recurrent *toxin-mediated perineal erythema* is another name for this condition, but since signs may occur elsewhere toxin-mediated erythema is probably a more appropriate title.

Necrotizing fasciitis

A rapidly advancing soft tissue infection resulting in necrosis of the subcutaneous tissue and fascia with systemic toxicity and high mortality, caused particularly by group A streptococci and *S. aureus*.

Aetiology

It frequently follows trauma, which is often trivial, surgery or a dental infection. It is more common in diabetics, the immunosuppressed, alcoholics and those with malignancy. Many organisms have been described in association with necrotizing fasciitis: type I necrotizing fasciitis involves aerobes and anaerobes and type II involves group A streptococci, which produce M proteins and pyrogenic exotoxins to give a local toxic effect and superantigens to cause systemic effects and streptococcal toxic shock syndrome. It is also associated with *S. aureus*.

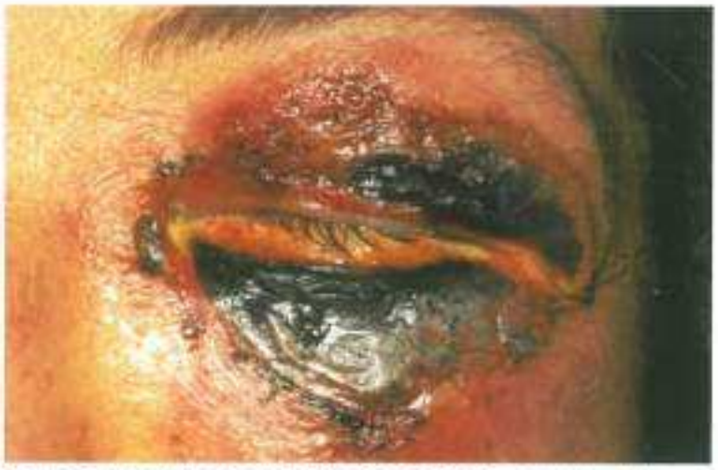


Fig. 13.24 Necrotizing fasciitis. There is localized painful erythema, which rapidly becomes oedematous with blistering and necrosis.

Clinical Features

Symptoms

There is a localized painful hot redness and swelling, rapidly progressing over a matter of hours to hypotension, high fever, tachypnoea, tachycardia, hypocalcaemia, altered mental state and collapse.

Morphology

It begins with erythema and oedema, progresses to cyanosis, blistering, necrosis (Fig. 13.24), gangrene and sloughing of the subcutaneous tissue.

Distribution

The lesion may occur anywhere on the skin, including genitalia, when it is sometimes termed *Fournier's gangrene*.

Management

The diagnosis is clinical. Aspirates should be Gram stained and cultured. Treatment is surgical and aggressive with debridement. Frozen sections of tissue should show polymorphs in the fascia and subcutaneous tissue. Rapid streptococcal diagnostic kits as used for throat infections are reported to be effective in identifying *S. pyogenes*. Supportive care and antibiotics, including penicillin and clindamycin, are indicated. Cephalosporins and erythromycin have been used. There is a significant mortality, which can be reduced, however, by prompt intervention.

Kawasaki disease

Also known as the *mucocutaneous lymph node syndrome*, it is an acute multisystem vasculitis that affects small and medium-sized blood vessels in young children. It presents with a high fever that lasts several days, a morbilliform rash with involvement of the conjunctivae, oral cavity, and cervical lymph nodes. The coronary arteries are involved if the condition is not treated promptly.

Aetiology

The disease was first described by Kawasaki in 1967; it is endemic in Japan affecting Asians generally but is uncommon in the UK and USA. It is slightly more common in males and has a peak incidence in the second 6 months of life but can occur in children until the age of 5 years. It is more common in the late winter and early spring. It is a leading cause of

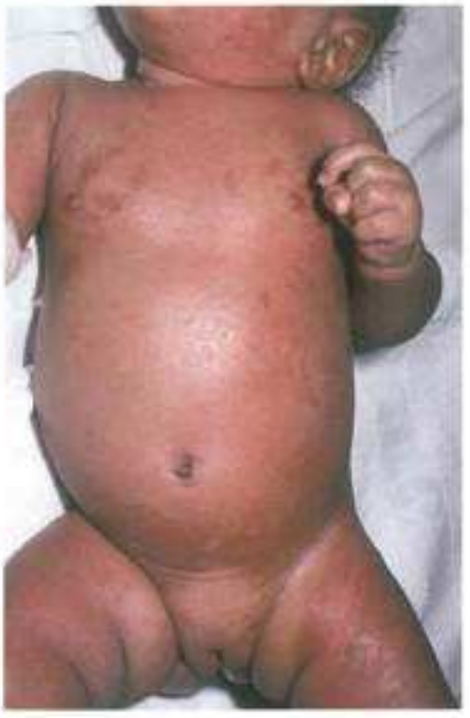


Fig. 13.25 Kawasaki disease. The exanthem is scarlatiniform and becomes extensive. It resolves with desquamation. Characteristically, the palms and the soles are involved and are tender. The child crawls to avoid walking.

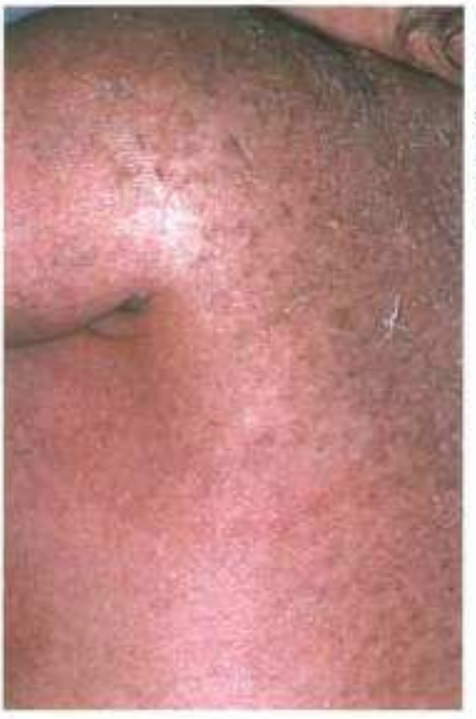


Fig. 13.26 Kawasaki disease. The child is ill, with a prolonged high remittent fever and cervical lymphadenopathy. Desquamation of the skin is striking by the 10th day.

acquired heart disease. There is an acute influx of polymorphs followed by lymphocytes and mononuclear cells involving all layers of the artery including the internal elastic lamina, resulting in aneurysms and thrombosis and ischaemia. There is increasing evidence that it is a toxin-mediated superantigen-driven disease. *S. aureus* (TSST-1) and occasionally *S. pyogenes* (SPE-B and SPE-C) have been isolated from the throat, axilla, groin and rectum of these patients. There is also marked expansion of Vβ-bearing T cells in acute but not convalescent sera, and this may explain why gammaglobulin, which contains antibodies that inhibit activation of T cells by superantigens, may be effective, but the case is not yet proven. Although siblings may be at risk within the first 10 days, person-to-person spread is uncommon. The condition occasionally recurs. It may be a disorder caused by an agent as yet unidentified in possibly a genetically predisposed individual.

Clinical Features

The patient is ill with a high remittent fever, persisting for 5 or more days and acute non-purulent cervical lymphadenopathy.

Morphology and distribution

Exanthem A tender polymorphous exanthem begins in the napkin area (Fig. 13.25), then gradually extends to the torso and extremities with reddening, oedema and induration of the palms and soles. Desquamation (Fig. 13.26) occurs by day 10.

Enanthem There is redness of the lips and oral cavity within 5 days. There is fissuring of the lips and protruberance of the papillae of the tongue as in scarlet fever. The pharynx is red and eroded. There is bilateral conjunctival (often sparing the limbus, the avascular zone around the iris) non-purulent injection.

Systemic

There are three phases to the disorder. The *acute febrile* phase lasts 7 to 14 days. In addition to the changes described above, the child is extremely irritable (much more so than in other illnesses), has a tachycardia and there may be aseptic meningitis, diarrhoea and hepatic dysfunction. The *subacute phase* lasts 10 to 24 days. The fever, rash and lymphadenopathy resolve but irritability, listlessness, loss of appetite and conjunctival injection may persist and the desquamation of the fingers and toes, particularly around the nails, is prominent. There may be arthritis, arthralgia and myocardial dysfunction and thrombocytosis during this period. During the *convalescent phase*, which lasts for 6–8 weeks, the erythrocyte sedimentation rate (ESR), which is universally raised, returns to normal.

Management

The differential diagnosis includes the staphylococcal scalded skin syndrome, toxic shock syndrome and scarlet fever. Leptospirosis and rickettsial infection, including Rocky Mountain spotted fever, should be considered. Viral exanthems such as measles where an exudative conjunctivitis may occur can be distinguished because the ESR and white cell count are low. Koplik spots may be present and a rapid IgM anti-measles titre may be measured.

Acute phase reactants (ESR and CRP) are universally raised, as is the white cell count with a neutrophilia. The platelets are normal in the first week but rise in the second. There is progressive normochromic/normocytic anaemia, hypoalbuminaemia and raised liver enzymes, especially alanine aminotransferase. The importance of the disease is in causing myocardial dysfunction, with the development of coronary aneurysms in approximately 20% of untreated patients; consequently, the diagnosis should be considered in any infant with a prolonged fever and rash. Electrocardiography should be performed at baseline and echocardiography used to monitor for the occurrence of coronary aneurysms.

Treatment is instituted to prevent the acute inflammatory vasculitis of medium-sized elastic arteries with its striking predilection for coronary arteries and aneurysm formation. Aspirin is given as an anti-inflammatory agent and to reduce platelet aggregation. Intravenous gammaglobulins, 2 g/kg as a single dose but repeated after 36 hours if still febrile, have significantly improved the prognosis if administered within the first days of illness.

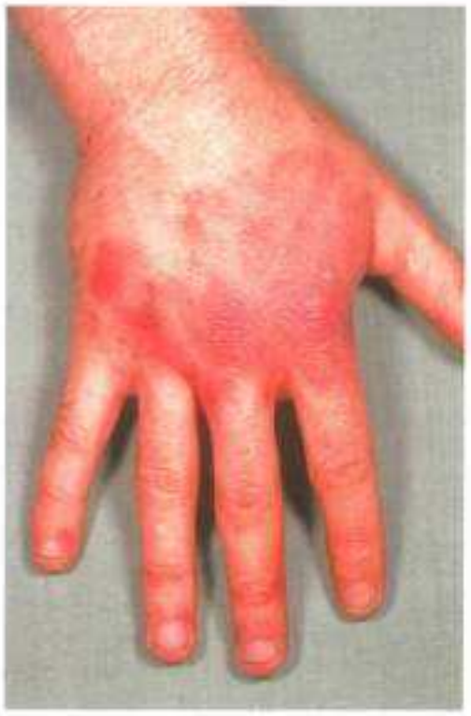


Fig. 13.27 Erysipeloid. A red, slightly oedematous eruption with a well-defined raised edge is present on the back of the hand. It is caused by *E. insidiosa* which gains access via a cut or abrasion.

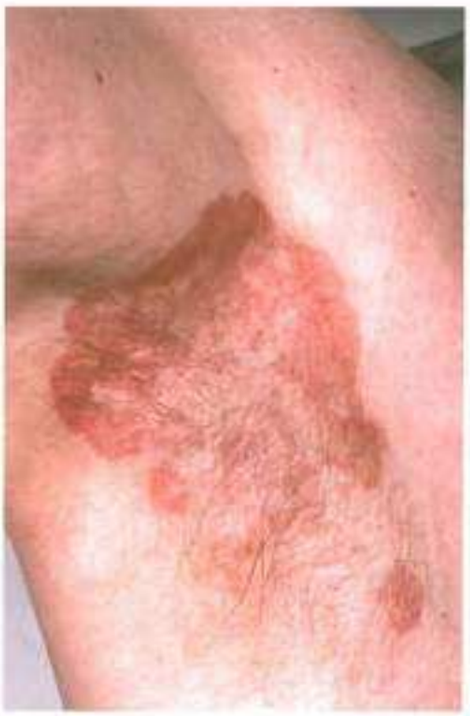


Fig. 13.28 Erythrasma. A brown discoloration is present in the axilla. The skin appears wrinkled and a fine scale may be visible.

Erysipeloid

An uncommon self-limiting localized infection with a Gram-positive corynebacteria, *Erysipelothrix rhusiopathiae*.

Aetiology

It usually occurs in those who handle contaminated raw fish or meat. The organism (which causes swine erysipelas) is inoculated into the skin through an abrasion causing symptoms 24–72 hours later.

Clinical Features

Symptoms

There is a slowly evolving pruritic or painful rash on the fingers that lasts a few weeks.

Morphology

A purple to red, slightly oedematous eruption occurs with a well-defined, raised edge (Fig. 13.27). It gradually heals. Unlike erysipelas, there is usually no systemic disturbance, although occasionally haematological dissemination causes arthritis and endocarditis.

Distribution

Usually on the hand.

Management

The condition responds to treatment with penicillin or erythromycin.

Erythrasma

An intertrigo caused by *Corynebacterium minutissimum*.

Aetiology

An intertrigo is any skin eruption that occurs between two apposing areas of the skin, such as the groins, axillae, under the breasts or between the toes. Erythrasma is one of the causes. It is most common in the obese, diabetics and in warm, humid environments. *C. minutissimum* is a short Gram-positive diphtheroid that is not easily cultured.

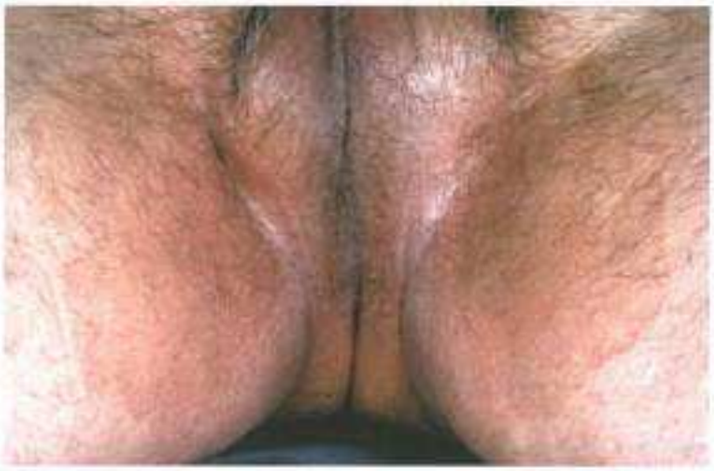


Fig. 13.29 Erythrasma. Intertriginous areas such as the groin are common sites because *C. minutissimum* favours a warm humid environment.

Clinical Features

Symptoms

It may be asymptomatic or itchy.

Morphology

There is a well-defined, brown discoloration with a fine, scaly, wrinkled surface (Fig. 13.28).

Distribution

Erythrasma is primarily a disorder of the flexures but may be more widespread (Fig. 13.29). It may occur between the toes and causes scaling, fissuring and maceration that is clinically indistinguishable from tinea.

Management

C. minutissimum produces porphyrins, which fluoresce a characteristic coral-pink colour under a Wood's light (Fig. 13.30). The diagnosis may also be made microscopically.

Topical therapy Sodium fucidate (2%), topical imidazoles and half-strength Whitfield's ointment are all effective.

Systemic therapy Erythromycin orally 250 mg four times daily for 5 days or erythromycin 1 g as a single dose are effective.

Trichomycosis axillaris

A *Corynebacterium* sp. infection of the axillary or pubic hair.

Aetiology

Most common in young males, it is largely a result of poor hygiene. The concretions of material which are found attached to the hair shaft are composed of masses of bacteria that belong to various *Corynebacterium* sp.

Fig. 13.30 Erythrasma. The organism fluoresces a coral pink under a Wood's light. (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

Clinical Features

Symptoms

Malodorous collections of material can be seen on the axillary hairs. Occasionally the sweat is discoloured red and stains clothing.

Morphology

Yellow collections of matter surround the hairs (Fig. 13.31). They are often an incidental finding.

Distribution

Axillary hair. Less commonly pubic hair.

Management

Shaving the affected hairs is usually enough, but clindamycin lotion, 1% aqueous formalin or benzoic acid compound are all effective. Daily washing of the area with soap and water usually prevents recurrences.

Pseudomonas infections

Ps. aeruginosa is an ubiquitous Gram-negative aerobic motile bacillus which thrives in an aqueous environment. It easily colonizes damaged skin, e.g. leg ulcers (Fig. 13.32), burns, otitis externa, chronic paronychia (Fig. 13.33) and the macerated skin between the toes, resulting in tropical immersion foot (*trench foot*). It is a frequent contaminant in the environs of patients in hospital, particularly in intensive care units, including polythene sheeting, bed pans and the hands of nurses. Ointments may also become colonized. Healthy individuals are little troubled by it but it may cause septicaemia in the immunocompromised. *Ecthyma gangrenosum* usually occurs during septicaemia, starting as haemorrhagic pustules or bullae that become ulcerated and surmounted by an eschar surrounded by an erythematous halo (Fig. 13.34). *Ps. aeruginosa* infection is particularly common in those with abnormal neutrophil function, for example with myelodysplasia or granulocytopenia. Mortality is high and therapy with recombinant granulocyte–macrophage colony-stimulating factor (molgramostim) has been advocated in addition to appropriate antibiotics such as ciprofloxacin and ceftazidime. In elderly diabetics and neutropenic patients, a cellulitis of the external ear (Fig. 13.35) may lead to necrosis, a

Fig. 13.31 Trichomycosis axillaris. Yellow concretions of material composed of masses of *Corynebacteria* sp. occur on the axillary hairs, usually in young males who do not wash properly.

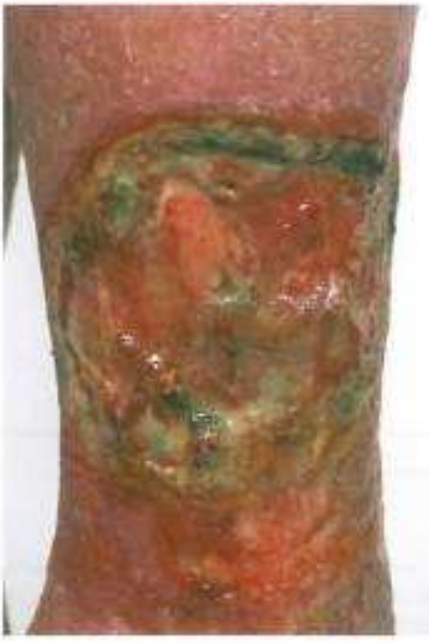


Fig. 13.32 *Pseudomonas* sp. contamination of a leg ulcer. Colonization of damaged skin by *Pseudomonas* is a common occurrence. A green discoloration is present.

condition known as *malignant external otitis*. A folliculitis may result from immersion in contaminated swimming pools or whirlpools. Infants are prone to peri-umbilical infections with the organism and may develop systemic infections in the high humidity environments of incubators.

Ps. aeruginosa produces two forms of pigment, pyocyanin (blue-green) and fluorescein (green-yellow). This discoloration may give a clue to the diagnosis.

PSEUDOMONAS FOLLICULITIS

An acute pustular eruption of the hair follicles caused by *Ps. aeruginosa*.

Aetiology

It may occur in the immunocompromised, but outbreaks of folliculitis from bathing in whirlpools contaminated with *Ps. aeruginosa* are common. Whirlpools are more difficult to maintain than swimming pools, as the chlorine evaporates more easily at high temperatures and with continual agitation of the water; there is also high bather usage per unit volume of water and thus the concentration of organic matter is increased, encouraging bacterial growth and reducing the chlorine to a less active form.

Clinical Features

Symptoms

An acute rash occurs, sometimes with a low-grade fever and lymphadenopathy.

Morphology

Crops of yellow pustules with surrounding erythema (Fig. 13.36) develop 24 to 48 hours after exposure.

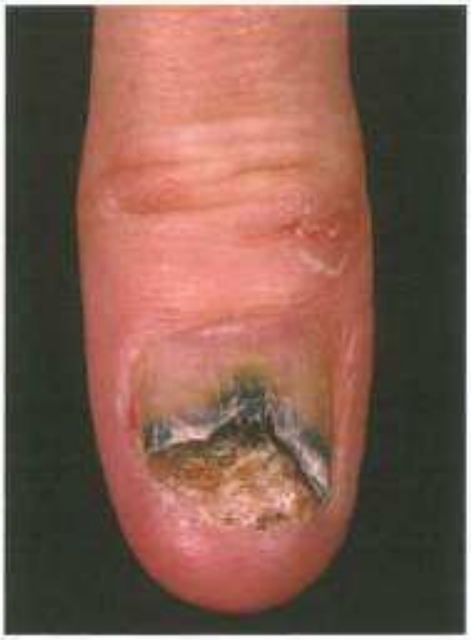


Fig. 13.33 *Pseudomonas* infection of the nail. The nail is dystrophic because of *Candida parapsilosis* infection and discoloured green because of infection with *Pseudomonas* sp.

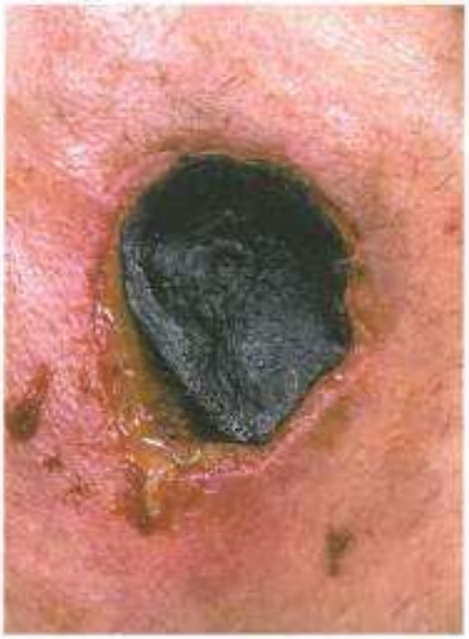


Fig. 13.34 Ecthyma gangrenosum. This man with lymphoma developed haemorrhagic blisters during *Pseudomonas* septicaemia; these became ulcerated and surrounded by an eschar with a red margin.

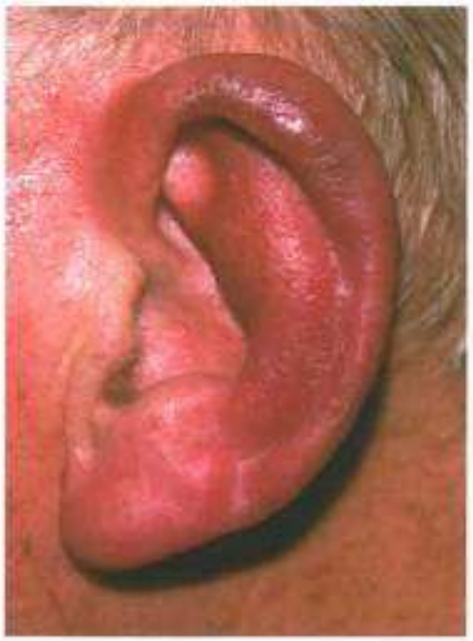


Fig. 13.35 *Pseudomonas* cellulitis. The ear is red, tender and oedematous. A swab revealed *Pseudomonas* sp. The condition responds to oral ciproxin.

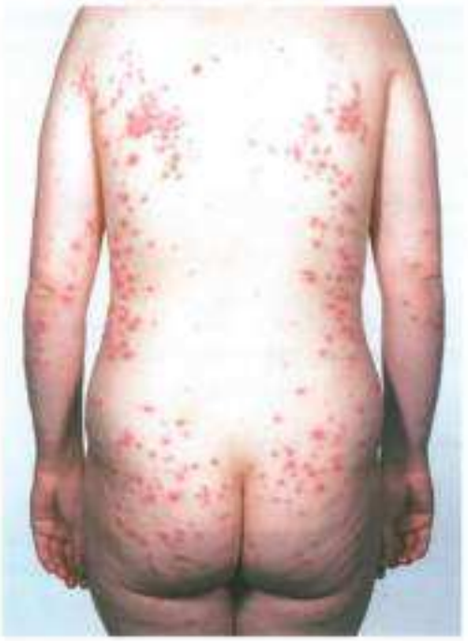


Fig. 13.36 *Pseudomonas* folliculitis. There are many yellow pustules surrounded by erythema. The growth of *P. aeruginosa* might suggest a source such as a contaminated whirlpool or immunosuppression.

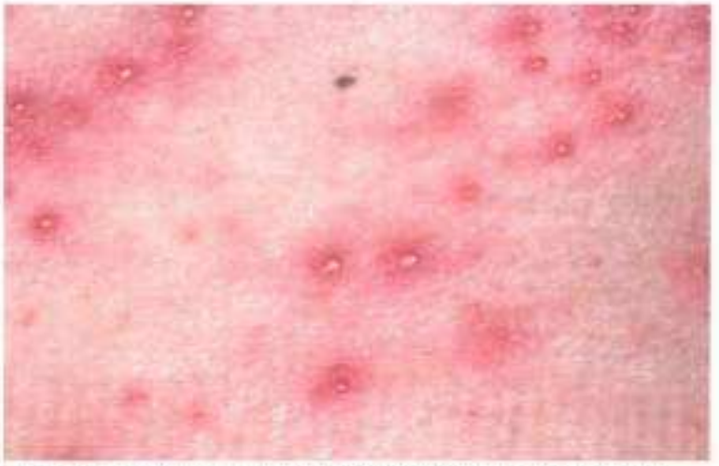


Fig. 13.37 *Pseudomonas* folliculitis. Widespread pustules surrounded by erythema may develop as a result of the use of contaminated whirlpools.

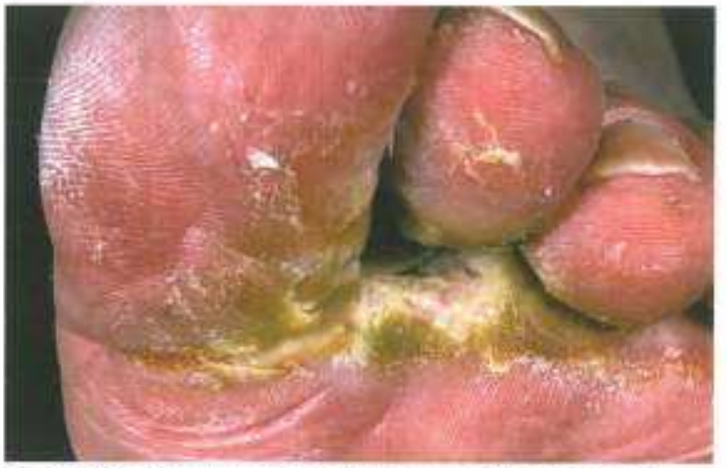


Fig. 13.38 *Pseudomonas* infection of the toe webs. There is a greenish sodden maceration between tightly compressed non-aerated toe webs, sometimes known as trench foot.

Distribution
The rash occurs mainly on the torso (Fig. 13.37) and limbs, and particularly under the areas covered by the swimming costume.

Systemic
Conjunctivitis, otitis externa, mastitis and urinary infections may also occur.

Management
A swab taken from a pustule should grow *Ps. aeruginosa* on culture and will give the clue to the diagnosis. Whirlpool folliculitis is self-limiting and passes within 10 days of exposure. Treatment may not be necessary but ciprofloxacin should be used in severe infections.

PSEUDOMONAS INFECTION OF THE TOE WEBS
An infection of macerated skin in the webs between occluded toes.

Aetiology
If the toes are closely apposed to one another, moisture and high humidity result in the skin becoming sodden (macerated) and colonized by *Ps. aeruginosa*. Patients have often used local bactericidal or fungistatic remedies that inhibit the organisms which would normally keep *Ps. aeruginosa* in check. Secondary invasion by *Candida albicans* may occur. Patients frequently have hyperhidrosis. It is not uncommon in acromegalics.

Clinical Features
Symptoms
A sodden, sometimes malodoriferous condition between the toes, often self-treated as athlete's foot.

Morphology
There is a sharply demarcated maceration of the skin, which may have a green tinge to it (Fig. 13.38). The area becomes eroded and raw.

Distribution
Between tightly compressed, non-aerated toe webs.

Management
Microbiological examination to exclude tinea and candidal infection and to establish the diagnosis of *Pseudomonas* infection is essential. Explanation of the lack of aeration that leads to the overhydration of the skin between the toes is important. Sensible leather footwear that allows for the proper circulation of air and limits excessive sweating and warmth of the foot is recommended. Heavy boots should be avoided. Potassium permanganate soaks are helpful, with careful drying of the toe webs afterwards, if necessary with a hairdryer. Topical antibiotics, for example polymixin or gentamycin, are not all that effective. Systemic therapy with ciprofloxacin and related drugs may be necessary.

Mycobacterial infections of the skin

Tuberculosis can occur in the skin as an infection caused either by direct inoculation or indirectly by lymphatic or haematogenous spread of *Mycobacterium tuberculosis* or *M. bovis* to the skin. Reactions may also occur in the skin secondary to the presence of mycobacteria elsewhere. Other mycobacteria that can infect the skin include *M. marinum*, which is contracted from infected fish, *M. ulcerans* (from infected soil), *M. fortuitum* and *M. chelonae* (from injections, and trauma including surgery), *M. kansasii* (in the immunosuppressed) and *M. avium-intracellare* complex (in AIDS and hairy cell leukaemia).

Mycobacteria are subdivided into slow and rapid growers on culture. The slow growers are known as photo-, scoto- or non-chromogens, depending on whether they produce a yellow pigment in the light (photo), in the dark (scoto) or not at all. Classical *M. tuberculosis* is a non-chromogen. Of the atypical mycobacteria, *M. marinum* and *M. kansasii* are slow-growing photochromogens and *M. avium-intracellare* complex and *M. ulcerans* are slow-growing non-chromogens. *M. fortuitum* and *M. chelonae* (and *M. abscessus*, which is now identified as being separate from *M. chelonae*) are rapid growers. *M. lepraе* is at present non-culturable.

TUBERCULOSIS OF THE SKIN
Human tuberculosis is caused by an acid-fast bacillus. *M. tuberculosis* and *M. bovis* are pathogenic to humans and animals but other *Mycobacterium* sp. may be pathogenic under special circumstances. *M. tuberculosis* is usually spread by droplet infection, the portal of entry being the lung; *M. bovis* usually enters through the intestine and much more rarely via the skin or mucous membranes. The bacillus travels via the lymphatics to the lymph nodes and then to the bloodstream. The primary infection in the lung consists of a granuloma (the Ghon focus) and enlarged hilar lymph

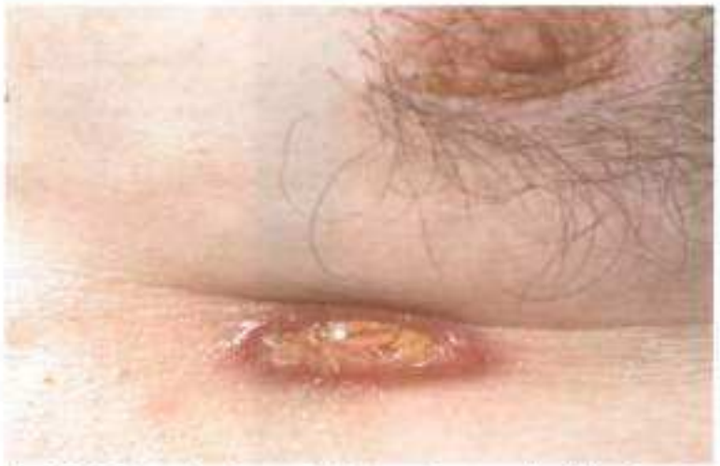


Fig. 13.39 Tuberculous chancre. It starts as a brown papule, which ulcerates and persists as a sore. The edge is undermined. The chancre occurs 2–4 weeks after direct inoculation.

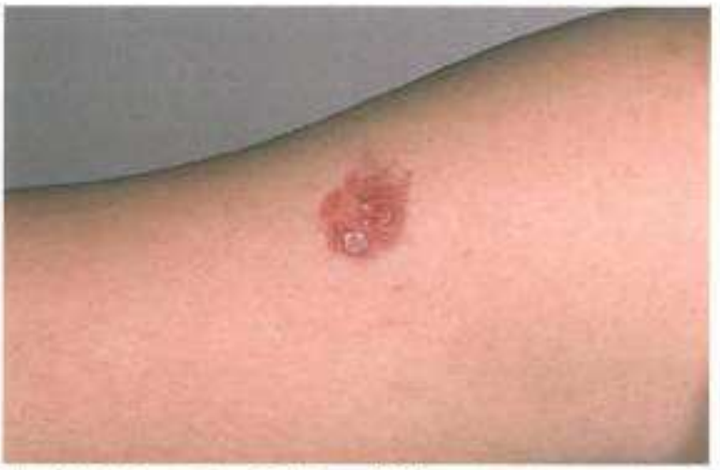


Fig. 13.40 BCG granuloma. The lesion of BCG granuloma ulcerates, scabs and persists as a sore. It heals with scarring after several months with calcification of the regional lymph nodes. This child had no previous exposure to TB.

nodes, which together are known as the primary complex. The tuberculin test is usually positive within a month or so and erythema nodosum and fever may occur at this time. The subsequent course varies according to the virulence of the mycobacterium and the resistance of the host. The disease may be arrested, progress or lie dormant to be reactivated in circumstances of immunosuppression.

Autoinoculation can occur in a patient with overwhelming advanced systemic tuberculosis. It usually occurs around the orifices, either the mouth and tongue from pulmonary organisms or around the genitalia and anus from intestinal disease (*Tuberculosis cutis orificialis*). Haematogenous spread to the skin may occur in acute miliary tuberculosis in infants and in the immunosuppressed, producing profuse crops of bluish and haemorrhagic papules and vesicles. Cutaneous reactions to tuberculosis elsewhere (known as tuberculids) may cause *erythema induratum*, lichen scrofulosorum or *papulonecrotic tuberculide*. They represent Arthus-like immune reactions within the skin, which become granulomatous secondary to haematological spread of *M. tuberculosis* or its antigen in a patient with positive TB cell-mediated immunity.

Tuberculosis and in particular cutaneous tuberculosis had become uncommon in developed countries because of improvements in living standards and the advent of effective drugs. However, since the advent of HIV infections and immunosuppressive drugs (including biologics), tuberculosis may be reactivated or atypical mycobacteria be acquired. The rare disorder of IL-12 interferon γ deficiency is associated with a genetic susceptibility to mycobacterial infections, including after BCG inoculation. Multidrug-resistant disease is also being reported, often because of insufficient treatment through lack of compliance by the patient.

TUBERCULOUS CHANCRE

Tuberculous chancres are the primary focus of a mycobacterial infection of the skin, occurring as a result of direct inoculation. Susceptible individuals are those who have never had a previous infection with *M. tuberculosis*; their Mantoux is negative.

Symptoms

A sore appears on the skin.

Morphology

Direct inoculation of the bacilli into the skin produces a chancre with associated lymphadenitis. The chancre starts as a brown papule, which frequently ulcerates and persists as a sore (Fig. 13.39). The edge of the ulcer may be undermined with an adherent crust on the surface.

Distribution

Primary tuberculosis may occur anywhere on the body but, since the bacilli are thought to be introduced via traumatized skin, it is usually seen on exposed parts, such as the face or limbs, particularly in children.

BCG GRANULOMA

A persistent sore after BCG (bacille Calmette–Guérin) vaccination.

Symptoms

A persistent sore after BCG vaccination.

Morphology

There is a granulomatous papule or plaque with a crusted centre.

Distribution

It occurs at the site of vaccination, on the upper outer arm (Fig. 13.40).

Management

The BCG should be given by intradermal injection into the upper arm in the sulcus over the insertion of the left deltoid muscle. A small papule occurs 2–6 weeks later, which discharges and heals as a scar. Keloids sometimes occur. In patients who have been previously vaccinated reactions, which include lupus vulgaris, an accelerated local reaction with regional adenitis, even progressing to scrofuloderma, abscess formation (particularly if it is injected too deeply) and tuberculids, may occasionally occur. Mild BCG granuloma may be treated with intralesional triamcinolone but systemic antituberculous therapy may be required for more active lesions.

LUPUS VULGARIS

A form of cutaneous tuberculosis that occurs in patients with some degree of immunity. It may be caused by inoculation of mycobacteria into normal skin, after BCG or following scrofuloderma. It may also result from lymphatic or haematogenous spread from a focus in a bone, joint or lymph node. Occasionally there may be multiple lesions, particularly from haematogenous spread in association with measles. After many decades, squamous cell carcinoma may develop.

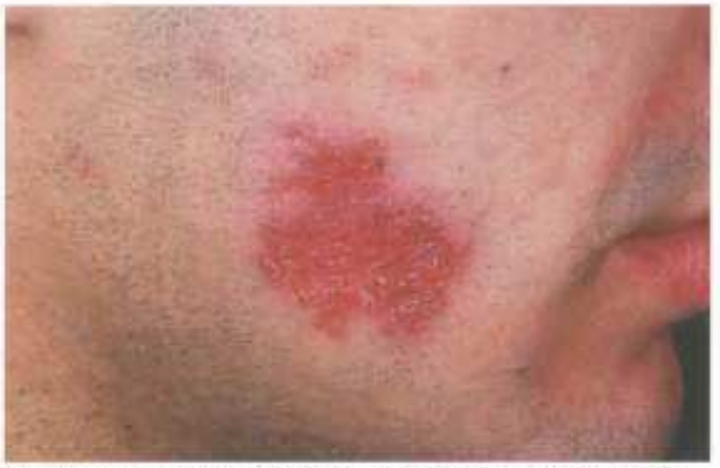


Fig. 13.41 Lupus vulgaris. The plaque is composed of papulonodules which when compressed with a glass slide displays a colour reminiscent of apple jelly. The cheek is the most common site.

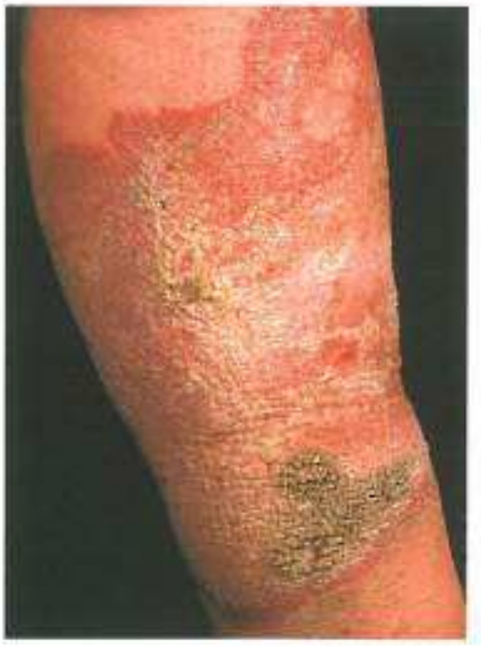


Fig. 13.42 Lupus vulgaris. The lesion is raised, well demarcated and warty. Skin biopsy for culture and histology can easily be performed.

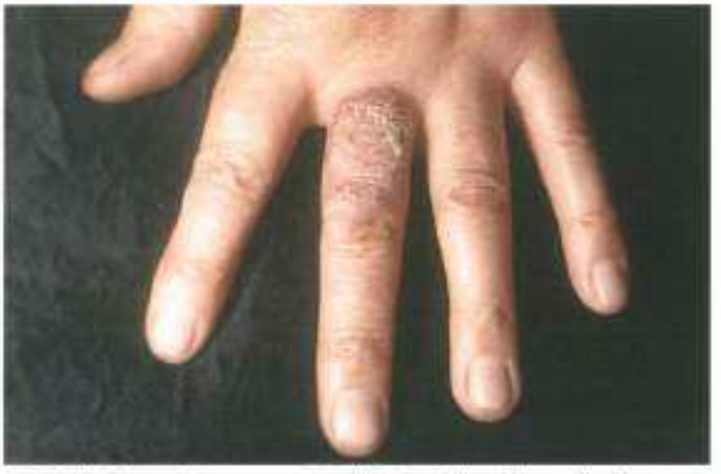


Fig. 13.43 Tuberculosis verrucosa cutis. This solitary lesion resulted from direct inoculation of tubercle bacilli into the skin from handling contaminated material. (Courtesy of the Institute of Dermatology.)

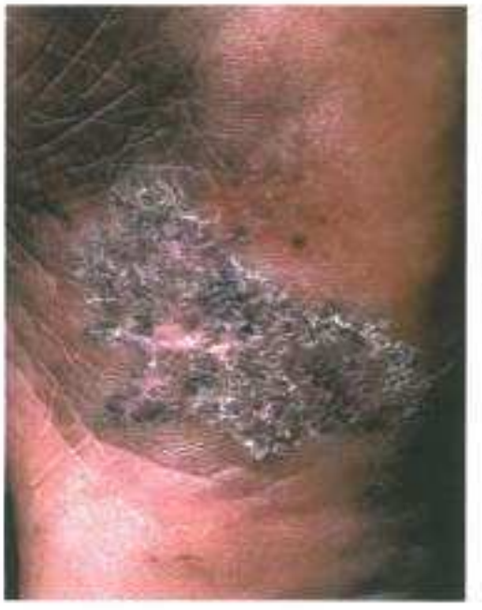


Fig. 13.44 Tuberculosis verrucosa cutis. This man acquired the infection in India through walking barefoot over contaminated soil. The diagnosis took 30 years to make and the condition was successfully eradicated with antituberculosis treatment.

Symptoms
There is a solitary patch on the skin, usually the face (Fig. 13.41) or a limb.

Morphology
It is a red-brown, somewhat raised, well-demarcated plaque. By pressing the lesion with a glass slide (diascopy), small nodules within the plaque appear as a translucent brown colour, somewhat reminiscent of apple jelly. Subsequently, the epidermis overlying the dermal granuloma becomes scaly and atrophic; ulceration and scarring may result.

Distribution
There is usually a solitary lesion on the face, neck or on a limb (Fig. 13.42).

TUBERCULOSIS VERRUCOSA CUTIS
This occurs in patients with previous exposure to tuberculosis and is a reinfection from direct inoculation into an abrasion from the soil as an occupational hazard in pathologists or butchers or injection of contaminated material (e.g. during ear piercing).

Symptoms
A single warty plaque develops.

Morphology
The lesion is usually a single, hyperkeratotic warty plaque (Fig. 13.43) with a red-brown colour, particularly at the margin.

Distribution
The lesion usually occurs on the hand or limb (Fig. 13.44).

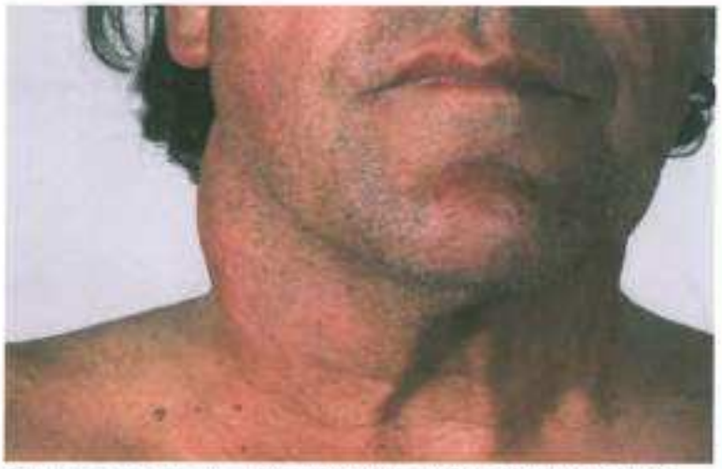


Fig. 13.45 Cold abscess. There is an obvious swelling in the right side of his neck. There is no inflammatory (hence it is 'cold' rather than hot) component.

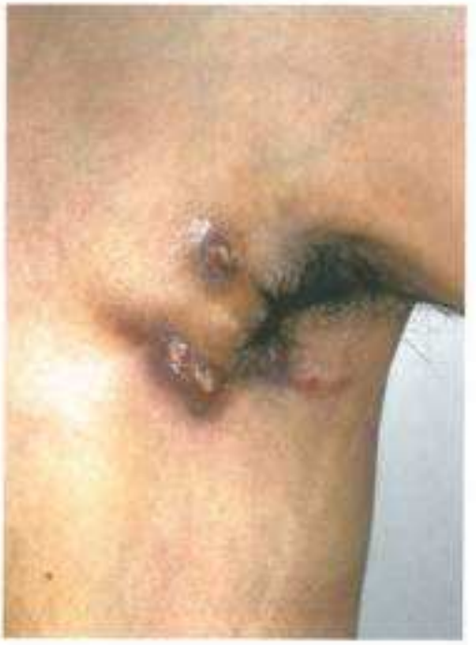


Fig. 13.46 Scrofuloderma. Direct extension to the skin has resulted from infected lymph nodes in the axillae, causing multiple ulcers with a bluish margin.

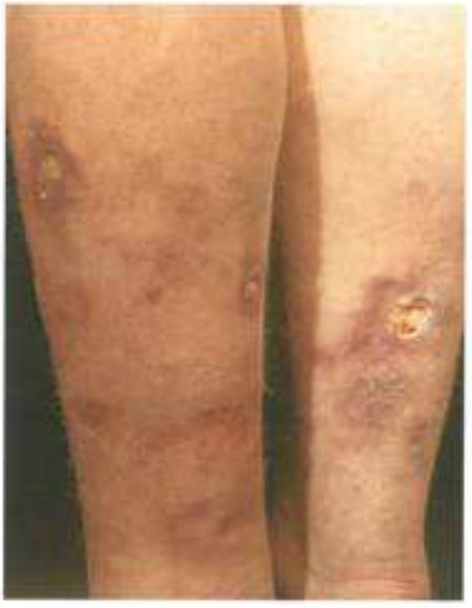


Fig. 13.47 Erythema induratum. Ulcerated tender nodules on the calves are suggestive of tuberculosis.

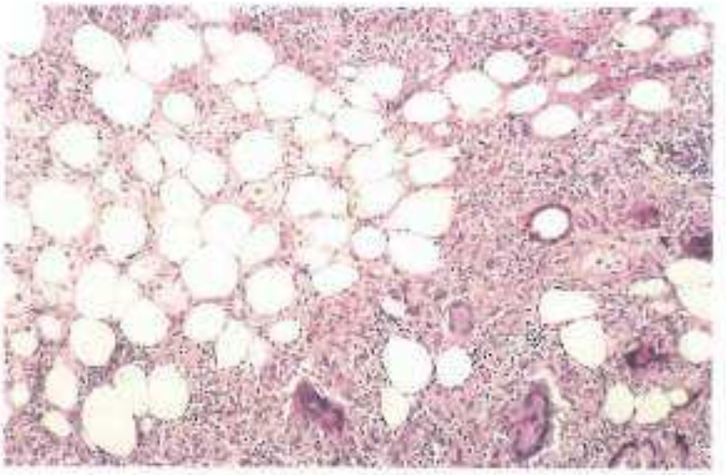


Fig. 13.48 Erythema induratum. On the left there is inflamed and necrotic fat with numerous foamy histiocytes (xanthoma cells). On the right, the inflammation is granulomatous with conspicuous giant cells.

SCROFULODERMA

This term describes direct extension of tubercle bacilli from an underlying infected lymph node or bone to the skin.

Symptoms

A discharging lump occurs in the neck (Fig. 13.45) or armpit (a 'cold abscess').

Morphology

A firm deep-seated subcutaneous nodule often with a blue, undermined edge (Fig. 13.46).

Distribution

The side of the neck, supraclavicular fossa or axillae are common sites.

ERYTHEMA INDURATUM (BAZIN'S DISEASE)

Symptoms

Painful lumps on the lower legs.

Morphology

The skin lesions are similar to those of erythema nodosum in that they are red, tender, warm nodules, but unlike erythema nodosum, they may ulcerate. There may be a concomitant fever and joint pains.

Distribution

The shins, ankles, feet and particularly the backs of the legs (Fig. 13.47) are affected. The upper limbs are occasionally involved.

Management

Erythema nodosum or erythema induratum are indications to search for tuberculosis elsewhere. A biopsy may be helpful (Fig. 13.48). Occasionally,

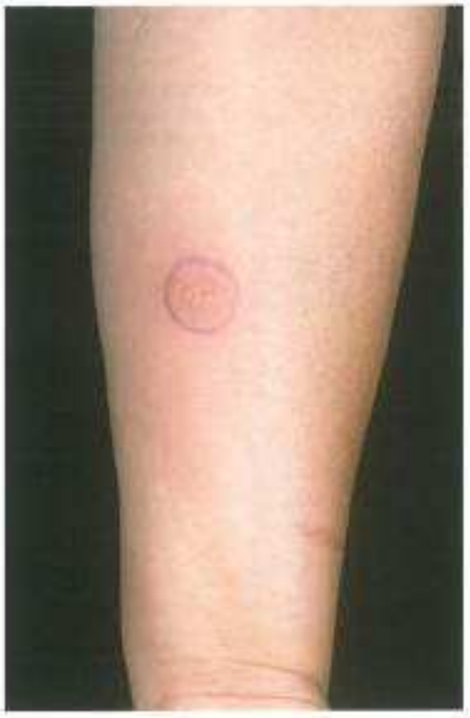


Fig. 13.49 Positive Mantoux test. Patients who have erythema nodosum without overt tuberculosis but have a strongly positive Mantoux test and a positive family history often respond to antituberculosis therapy.

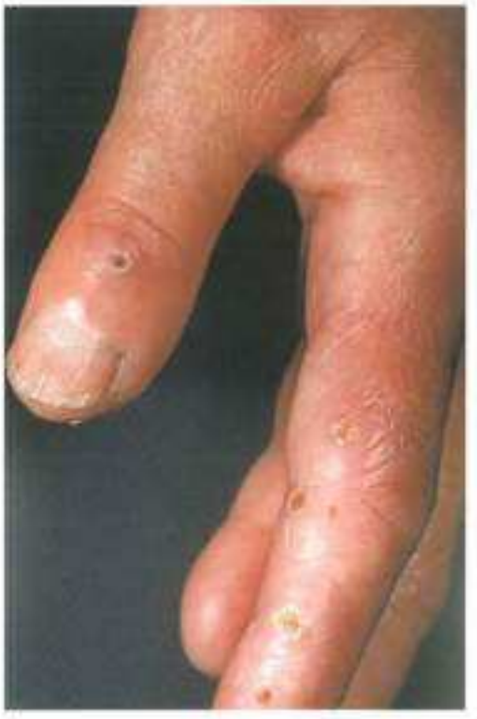


Fig. 13.50 Papulonecrotic tuberculide. Crops of necrotic indolent papules occur particularly on the extremities.

no overt focus of tuberculosis is found in erythema induratum and yet the Mantoux test may be strongly positive (Fig. 13.49) and there may be a family or personal history of tuberculosis. This form of tuberculid without overt evidence of tuberculosis may, however, respond to antituberculous therapy.

TUBERCULIDS

The validity of these eruptions as manifestations of tuberculosis is still debated but they include papulonecrotic tuberculide, lichen scrofulosorum (a very rare eruption of tiny follicular pink or yellow-brown papules with a slight scale occurring mainly on the trunk, which disappear without scarring especially in children with nodal or skeletal TB) and nodular vasculitis. Papulonecrotic tuberculide (Fig. 13.50) is the most common. There are indolent dusky red papules or papulopustules which heal with scarring, occurring in crops fairly symmetrically on the extensor surfaces of the limbs and buttocks.

Atypical mycobacteria

M. kansasii usually infects the lung but very occasionally involves the skin in the immunosuppressed, particularly those who have had renal transplants. It produces verrucous, nodular, cellulitic, sporotrichoid or papulonecrotic lesions. *M. avium-intracellulare* complex is an opportunistic mycobacterium seen in the immunosuppressed. It is ubiquitous in nature and gains entry via the lungs or gut and does not need inter-human transmission. The primary infection is usually in the lung and disseminates in those with AIDS with a $CD4^+$ cell count less than 50×10^6 cells/l, haematological malignancies (particularly hairy cell leukaemia), connective tissue disorders and in those taking immunosuppressive drugs, particularly systemic steroids. It causes pustules, abscesses, nodules and ulcers on the skin. The rapid growers (*M. fortuitum*, *M. chelonae* and *M. abscessus*) are present in water and the soil and usually contaminate wounds, including surgical. They are seen in the immunosuppressed although not particularly in those with AIDS. They particularly cause abscesses (Fig. 13.51), sometimes with sporotrichoid spread following injections, including repeated injections in diabetics. Other sources of trauma, for example, wounds (particularly during the Vietnam War), surgery and catheterization may permit entry of these organisms. *M. marinum* is an acid-fast bacillus that causes tuberculosis in fish. It can infect through breaks in the skin from contaminated fish-tanks or swimming pools. It is described here.

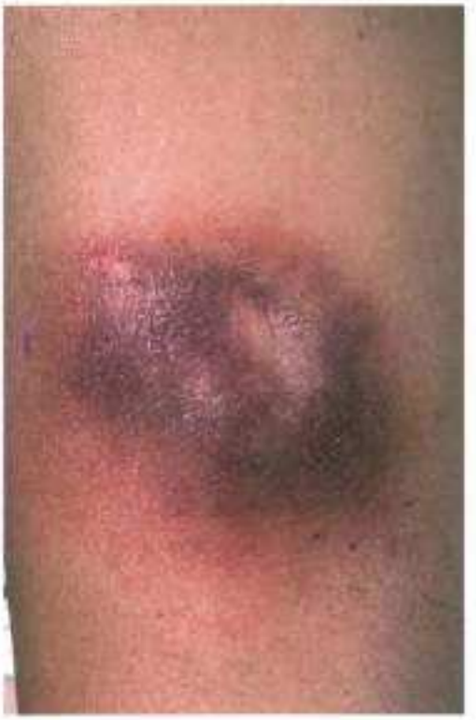


Fig. 13.51 *Mycobacterium fortuitum*. There is a mauve nodule. Biopsy for pathology and culture is essential for diagnosis. *M. fortuitum* is usually seen in the immunosuppressed.

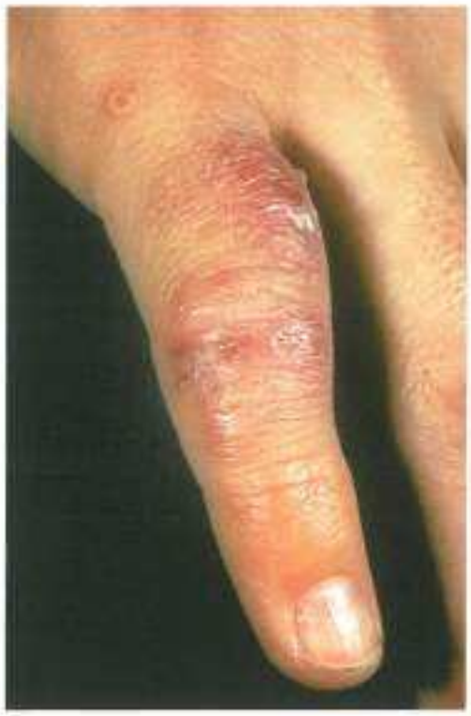


Fig. 13.52 Fish-tank granuloma. This man cut his skin on an aquarium that had contained fish which died of *Mycobacterium marinum* infection. Enthusiasts who siphon off their tanks may develop pulmonary symptoms. (Courtesy of St Bartholomew's Hospital.)

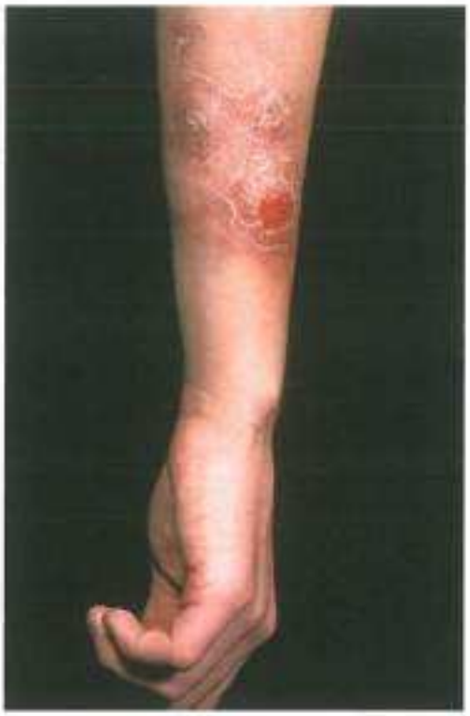


Fig. 13.53 Fish-tank granuloma. Red nodules ascending in a 'sporotrichoid' manner are present on the forearm, following an abrasion whilst cleaning a fish-tank.

FISH-TANK AND SWIMMING POOL GRANULOMA

An infection in a skin abrasion caused by *M. marinum* (syn. *balnei*) from contaminated water.

Symptoms

The patient may have cut the skin in a swimming pool or whilst cleaning out a fish-tank after the fish had died.

Morphology

Purple-red nodules develop at the site of injury (Fig. 13.52) and appear along the line of lymphatic drainage in a sporotrichoid manner (Fig. 13.53) from the inoculation site. They usually heal spontaneously after a number of weeks or months.

Distribution

Anywhere but usually the finger, hand or face.

Management

The diagnosis is made by skin biopsy. The histopathology is granulomatous and the bacillus can be grown in culture if incubated at 31 °C and not the usual 37 °C required for other mycobacteria. There is no specific effective treatment, but success has been reported with rifampicin, septrin, minocycline, ethambutol, ciprofloxacin and clarithromycin.

Histopathology of Mycobacterial Infections

There is non-specific inflammation in the early stages of the skin lesion but tubercle formation occurs within a month. A tubercle granuloma consists of foci of epithelioid cells containing a variable but usually sparse number of Langerhans' giant cells with a surrounding mononuclear cell infiltrate (Fig. 13.54). Centrally, there is caseation necrosis, which may calcify. There are accompanying endovascular and perivascular changes that result in fibrosis. The histological changes and the finding of bacteria are the result of a balance between the organism and the immunological response, rather like in leprosy. In miliary orificial tuberculosis, there are numerous bacilli to be found, but bacilli are rarely found in the fully formed tubercles and have to be cultured. In scrofuloderma where the cell-mediated immune response is poor, a few bacilli may be found and likewise in BCG granuloma. No bacilli are usually identified in lupus vulgaris. Culture is necessary to differentiate which mycobacteria is responsible for the infection. The differentiation of tuberculous granuloma from other causes of granuloma, in particular sarcoidosis, may not be easy, but in general in:

- sarcoidosis: no caseation necrosis occurs
- tuberculoid leprosy: neural and perineural involvement occurs
- leishmaniasis, blastomycosis and chromomycosis: the causative organism should be identifiable
- tertiary syphilis: there is a more pronounced vascular involvement and a plasma cell infiltrate is present.

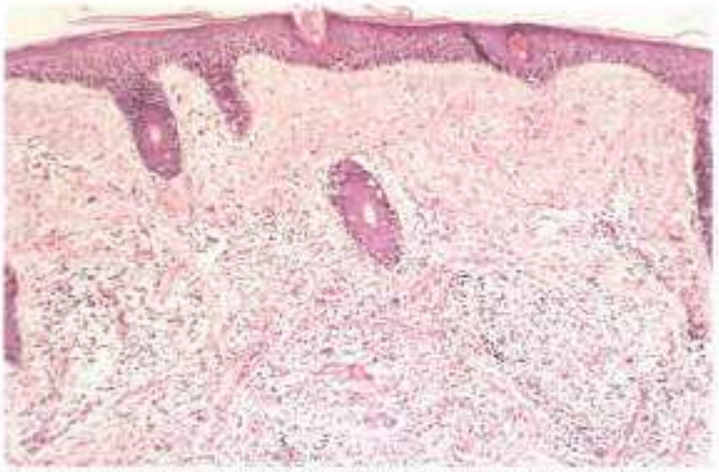


Fig. 13.54 Lupus vulgaris. An ill-defined granulomatous infiltrate containing giant cells and lymphocytes is situated in the upper dermis, in close proximity to a hair follicle. Caseation necrosis is absent. Such features are highly suggestive of lupus vulgaris.

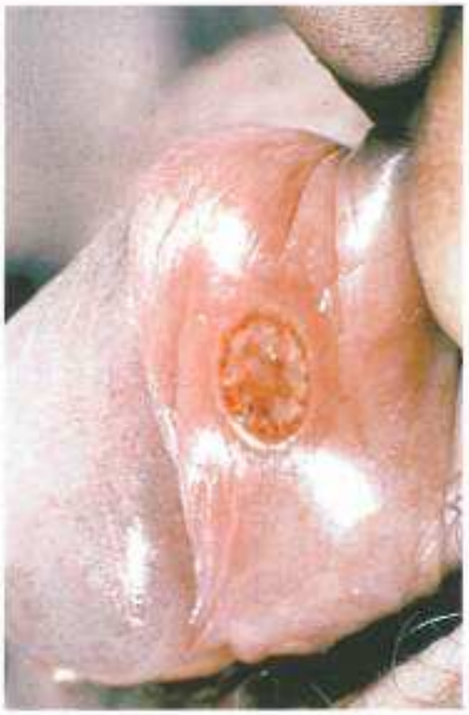


Fig. 13.55 Primary syphilis. The chancre is a painless ulcer with an indurated edge and a yellow base. (Courtesy of Dr Fred Lim.)

Fig. 13.56 Dark field examination showing treponemes. A typical corkscrew appearance of a spirochaete is visible in the primary and sometimes secondary stages of syphilis (From Morse et al. Atlas of Sexually Transmitted Diseases and AIDS, 4th Edn. London: Saunders; 2010. p131. Figure 7.8S. Courtesy of David Cox.)

Management of Mycobacterial Infections

The diagnosis of cutaneous mycobacterial infection may be difficult because a large number of acid-fast bacilli must be present for them to be seen histopathologically. They are virtually never seen in lupus vulgaris because of the high immunological resistance to the bacillus. Equally, tuberculin testing does not distinguish between active and previous tuberculosis and in some forms may actually be negative. Culture is the gold standard (particularly to determine sensitivities) but culture of the slow-growing mycobacteria may take 6 weeks although rapid growers are positive within 7 days. The polymerase chain reaction (PCR) involves amplification of mycobacterial target sequences and is a rapid diagnostic tool because only a few mycobacterial genomes need be present. It has now been used to identify the presence of bacilli in lupus vulgaris, scrofuloderma, accidental exogenous inoculation and orificial tuberculosis. Equally importantly, it has been found in the tuberculids where culture was virtually always negative, which is a major advance in understanding these conditions and in separating the real tuberculids from conditions that have been wrongly attributed to tuberculosis in the past, such as lupus miliaris disseminatis faciei.

The patient should be fully examined to search for the source of extrapulmonary disease. Underlying accompanying disease such as alcohol misuse, HIV and diabetes should be treated. The four drugs that are routinely employed are isoniazid, rifampicin, pyrazinamide and ethambutol. There are various recognized protocols and these are sometimes modified to suit local conditions, particularly in view of the expense of some of the drugs. Therapeutic failures are frequent because of lack of compliance. BCG vaccination should be offered to all children between the ages of 10 to 13 years, to tuberculin-negative children of immigrants from countries where tuberculosis is endemic, to health workers and to travellers. Patients with erythema induratum and strongly positive Mantoux tests without evidence of tuberculosis elsewhere should be treated with full dosage antituberculous therapy.

Syphilis

A sexually acquired infection with the spirochaete *Treponema pallidum*, commencing as a sore at the site of inoculation with localized lymphadenopathy, it subsequently affects mucocutaneous surfaces and if untreated may involve the cardiac and nervous systems in its tertiary stage.

Aetiology

Syphilis is usually transmitted sexually, particularly among homosexual men, but may be acquired from maternal disease in utero or from infected blood products or instruments. The disease is divided into primary, secondary, latent or tertiary stages. The first two are infectious. If untreated, it may progress through all four stages or remit. Concomitant HIV facilitates acquisition of syphilis.

PRIMARY SYPHILIS

Clinical Features

Symptoms

A sore (chancre) occurs at the site of inoculation, 10–100 days later.

Morphology

The chancre is a painless ulcer with an indurated edge (Fig. 13.55). The base is yellow and harbours a large number of spirochaetes, which may be demonstrated by dark-field microscopy (Fig. 13.56). It heals spontaneously, often without trace, within 1–3 months.

Distribution

The lesions are usually seen on the genitalia or around the anus but can occur anywhere, particularly the lips, inside the mouth, cervix, rectum or finger. There is painless local lymphadenopathy.

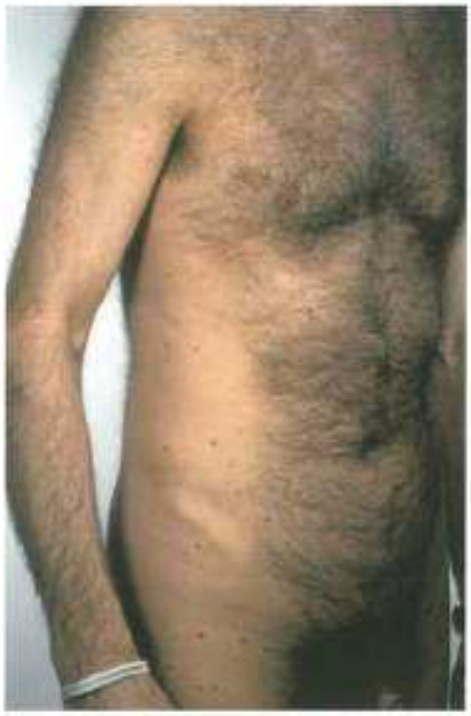


Fig. 13.57 Secondary syphilis. Initially, the rash is macular and pink and is most obvious on the trunk. It does not itch. The serology is positive at this stage.

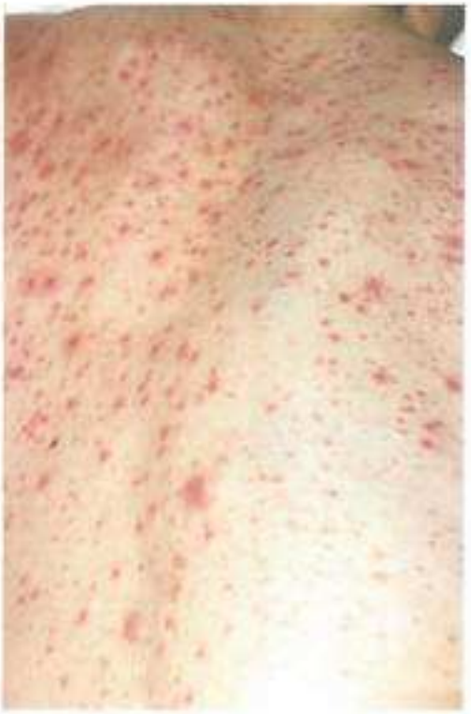


Fig. 13.58 Secondary syphilis. The lesions become papular and tend to crop. (Courtesy of St Mary's Hospital.)

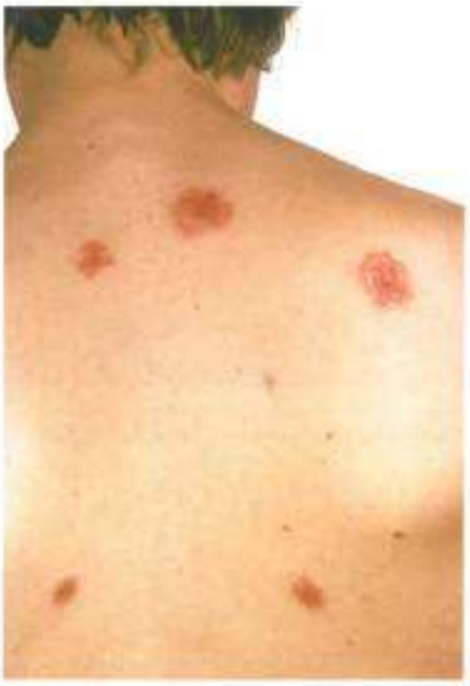


Fig. 13.59 Secondary syphilis. In the later stages, brown nodules may occur. Syphilis is uncommon in women. This woman's husband was bisexual and was the source.

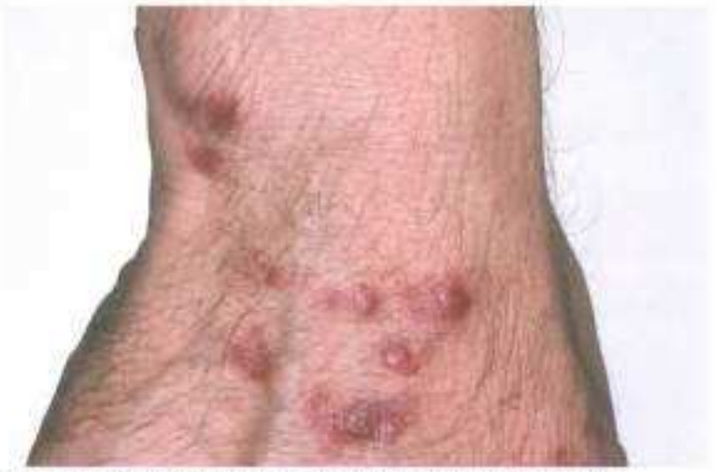


Fig. 13.60 Secondary syphilis. The nodules are present in an annular configuration. A skin biopsy may aid diagnosis.

SECONDARY SYPHILIS

Clinical Features

Symptoms

Most patients are diagnosed during the primary stage. However, if the chancre is not visible to the patient, either around the anus, in the rectum or on the cervix, the disease may evolve to the secondary stage. This occurs about 2 months after the chancre.

The patient is feverish, unwell and presents because of a non-itchy rash.

Morphology

Initially the rash is macular and pink (roseola) and is most obvious on the trunk (Fig. 13.57). It becomes papular and more widespread (Fig. 13.58). There is a tendency to cropping of lesions. The papules become brown and may resemble pityriasis rosea or psoriasis. Later, they may become more infiltrated (Fig. 13.59). Annular configurations may occur (Fig. 13.60). The primary lesion may still be visible. Occasionally, circumscribed areas of *anetoderma* occur on the trunk in the secondary, latent or tertiary stages. The skin feels slack (Greek, *anetos*) on palpation because of an absence of dermal substance, with loss of elastic tissue histologically. Anetoderma also occurs in lupus erythematosus or as a primary defect.

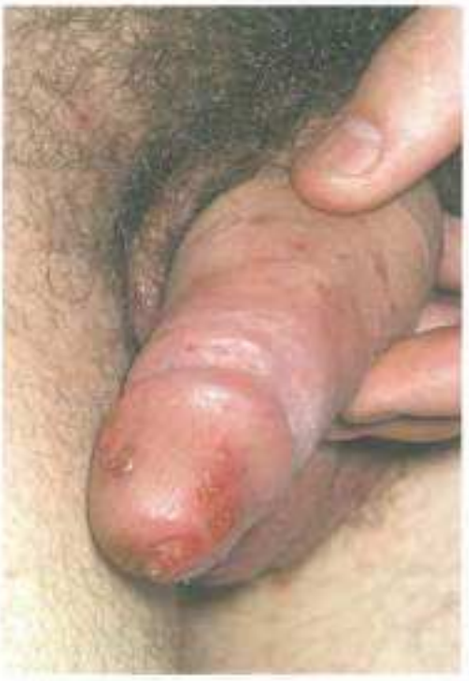


Fig. 13.61 Secondary syphilis. Moist erosions are present. The genitalia are usually involved. (Courtesy of St Mary's Hospital.)

Fig. 13.62 Secondary syphilis. Brown lichenoid papules are present on the penis. Secondary syphilis is not itchy.

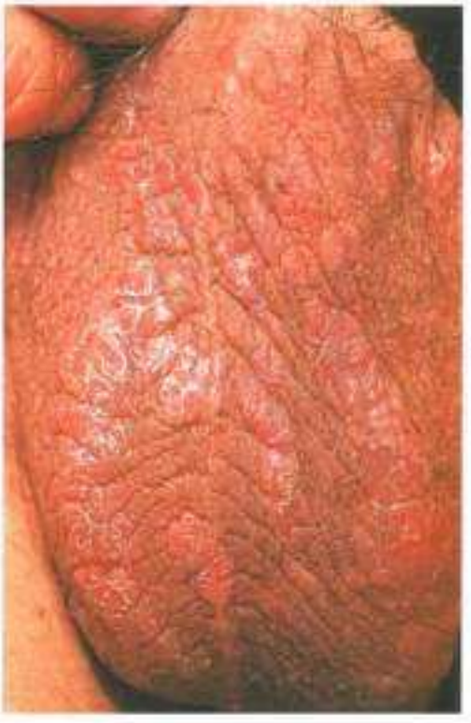


Fig. 13.63 Secondary syphilis. Scaly, red, firm patches are present on the scrotum.

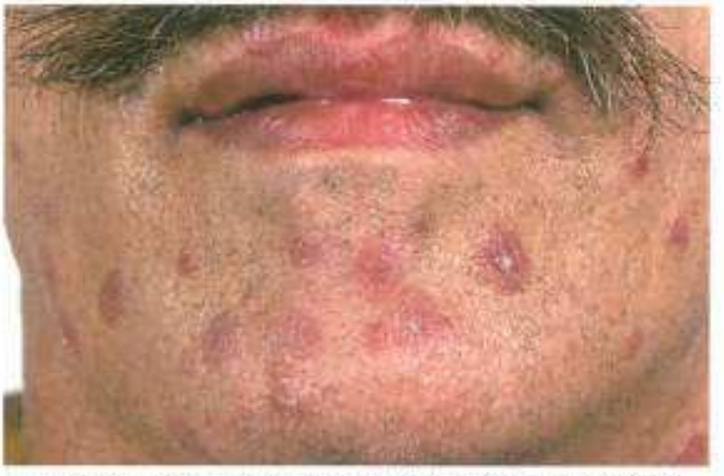


Fig. 13.64 Secondary syphilis. The face is usually involved. The papules and plaques may become scaly and are well defined. This is the same patient as in Figure 13.57.

Distribution

The eruption is widespread and particularly involves the genitalia including the penis (Figs 13.61 and 13.62) and scrotum (Fig. 13.63), face (Fig. 13.64), palms (Fig. 13.65) and soles (Fig. 13.66). The lesions may be more profuse around the frontal hair margin and sides of the neck, known, respectively, as the crown (Fig. 13.67) and collar of Venus. In the intertriginous areas, the papules may become eroded (condylomata lata). Condylomas mainly occur around the anus or in the groin but may occur under the axillae or breasts, in the umbilicus or between the toes. These lesions are usually moist and exude treponemes in the serum; they are, therefore, highly infectious.

Slightly raised, oval patches with an off-white, eroded surface (Fig. 13.68) occur on the mucous membranes. The tongue (Fig. 13.69), lips, inside of the mouth, soft palate and fauces are most usually involved. Several contiguous lesions are known as 'snail-track' ulcers. Hair loss is common, either as part of the cutaneous eruption (Fig. 13.70) or, subsequently, as a telogen effluvium response to the systemic upset.

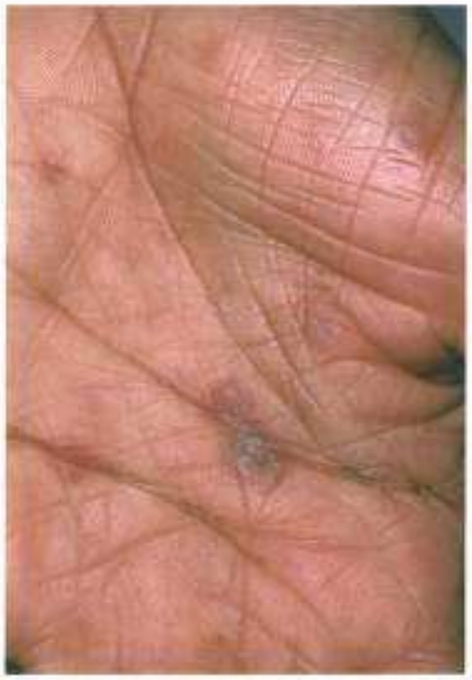


Fig. 13.65 Secondary syphilis. Discoloured macules were present on the palms of this 17-year-old West Indian girl.

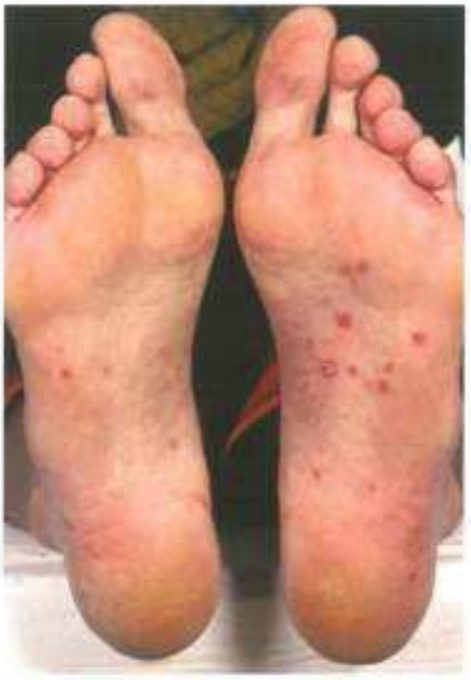


Fig. 13.66 Secondary syphilis. The soles are usually affected with papules.

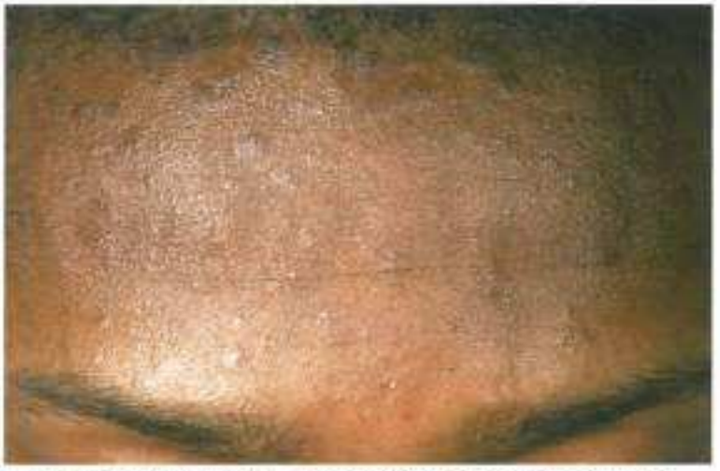


Fig. 13.67 Secondary syphilis. There are brown, non-pruritic, slightly raised lichenoid papules around the forehead and hairline, with patchy alopecia.

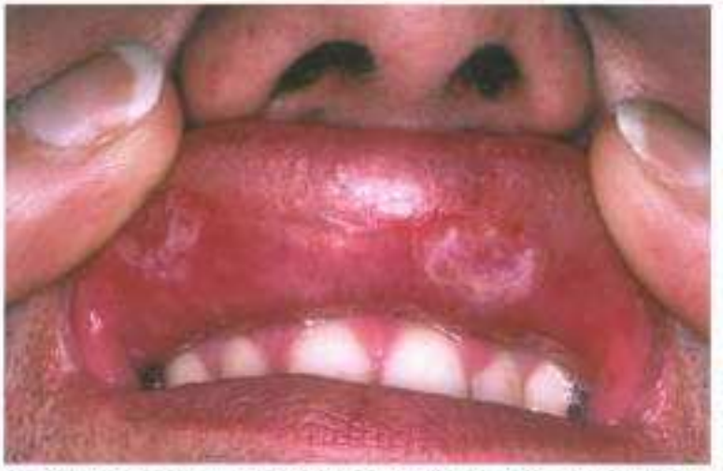


Fig. 13.68 Secondary syphilis. White, slightly eroded patches are present inside the upper lip. (Courtesy of Dr Barry Monk.)

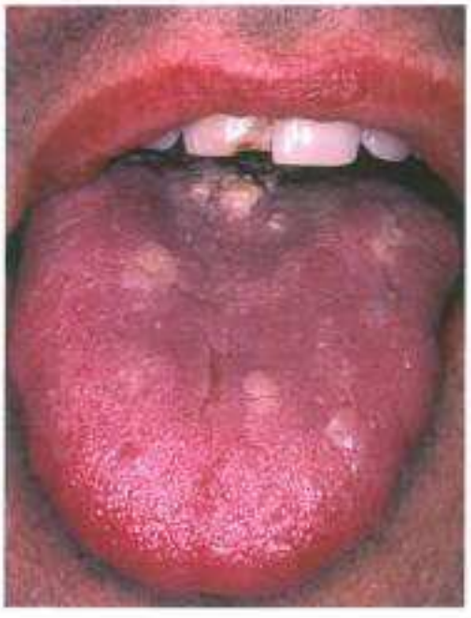


Fig. 13.69 Secondary syphilis. There are several slightly raised, oval, whitish patches on the dorsum of the tongue.

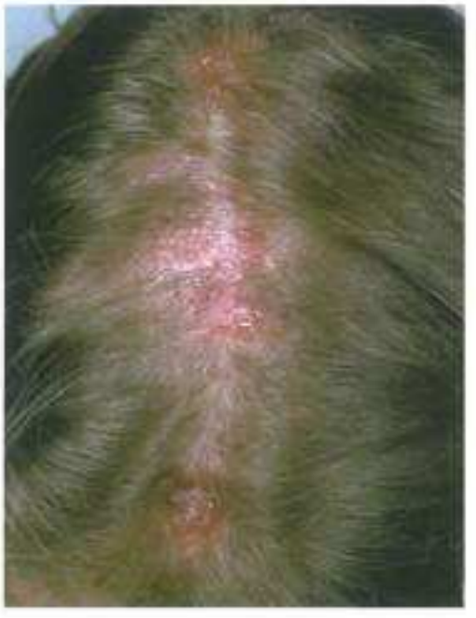


Fig. 13.70 Secondary syphilis. There are patches of erythema, scaling and alopecia in the scalp.

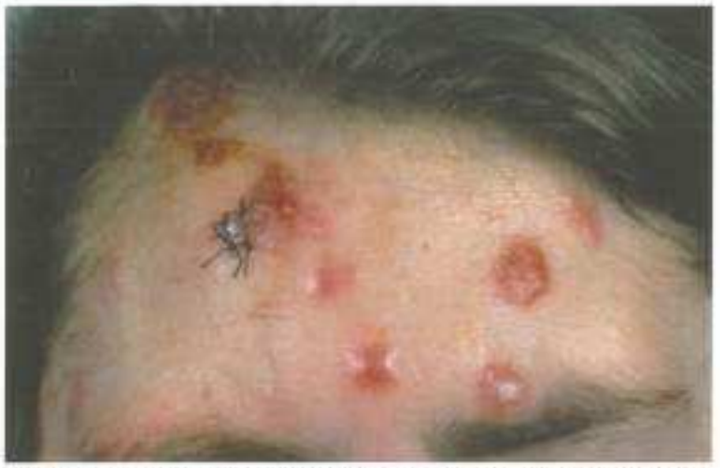


Fig. 13.71 Lues maligna. Red brown nodules occur which may become eroded or ulcerated.

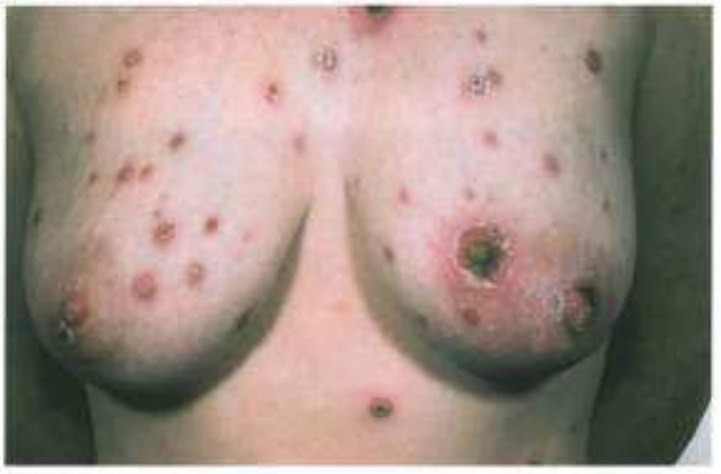


Fig. 13.72 Lues maligna. A rare ulcerative nodular form of secondary syphilis may occur in association with HIV infection. (Courtesy of Dr Daniel Creamer.)

A rare ulcerative and nodular (Fig. 13.71) form of secondary syphilis may occur in association with HIV infection. It is known as *Lues maligna* (Fig. 13.72).

Systemic features

The patient may not be ill at all, but most have some degree of malaise. Headache, sore throat, hoarseness, deafness, photophobia, neck stiffness, polyarthritis and nocturnal bone pains may all occur. There may be renal involvement and hepatitis, which may account for pruritus, which otherwise is classically absent in secondary syphilis unless there is a complicating factor such as hepatitis or a second acquired disease such as scabies. Generalized lymphadenopathy is usual. Anaemia, leucocytosis and a raised ESR are common. At this stage, the serological tests are positive.

SECONDARY RELAPSE AND LATENT SYPHILIS

If untreated, the patient recovers but with a variety of possible sequelae. There may be a secondary relapse of a mucocutaneous nature within 2 years, particularly affecting the genitalia, palms and soles. This stage is still infectious. The disease then passes into a latent asymptomatic phase, but with positive serology. Even during this phase, seronegative conversion and spontaneous cure may occur. If it does not, the disease may proceed to cardiovascular or neurosyphilis or other organ involvement. This is known as tertiary syphilis.

TERTIARY SYPHILIS

Clinical Features

Symptoms

Asymptomatic annular patches appear.

Morphology

The gumma is the hallmark of tertiary syphilis. It is a chronic granuloma that develops a number of years after the primary inoculation and is non-infectious.

There are firm brownish-red papules or nodules, which are usually arranged as an annular plaque. They are asymmetrical and sparse, even solitary (Fig. 13.73). Their surface is smooth or scaly, in which case they may resemble psoriasis (Fig. 13.74). They heal with scarring. Subcutaneous lesions may break down and ulcerate. The ulcer is several centimetres in diameter and has a vertical punched-out wall (Fig. 13.75). The base has a yellow slough rather like a chamois leather.

Distribution

These lesions occur particularly over the upper shins, the chest, face and scalp. Mucosal gummas may occur and the tongue may be diffusely infiltrated, with white patches, erosions and fissuring. Mucosal lesions may be premalignant.

Systemic features

Neurosyphilis occurs in the tertiary stage either due to an endarteritis or direct treponemal invasion. It results in hemiparesis, tabes dorsalis (diplopia, lightning painful paraesthesias of the extremities, ataxia, sphincter disturbance, abdominal, rectal and laryngeal pain [visceral crisis] and Argyll–Robertson pupils), and dementia. Cardiovascular syphilis results from endarteritis of the vasa vasorum of the proximal aorta.

CONGENITAL SYPHILIS

Congenital syphilis is rare where routine antenatal care demands serological examination of all expectant mothers. The result of transplacental infection depends on the immunological maturity of the fetus and the degree of infection. Early in pregnancy, abortion or stillbirth is the rule and the fetus may be covered in blisters. If pregnancy progresses to a later stage, the child may be born with papules and blisters on the palms and soles, or born healthy with subsequent failure to thrive, an eruption similar to secondary syphilis, hepatosplenomegaly and pulmonary and bone involvement. Late congenital syphilis presents in childhood with tertiary-like manifestations known as stigmata. They include perforation of the palate and collapse of the nose as a result of gummas, and frontal bossing and bowing of the tibia owing to periostitis. In addition, there may be nerve deafness, abnormal teeth (notched incisors, widely spaced peg shapes and mulberry molars) and interstitial keratitis (Hutchinson's triad) as well as joint effusions. Neurosyphilis may eventually result.

Histopathology of Syphilis

There is a heavy infiltration of the dermis with lymphocytes and plasma cells (Fig. 13.76), including around blood vessels; this is associated with intimal proliferation in both arteries and veins (endarteritis obliterans). *T. pallidum* may be found in sections at the primary syphilis stage but not usually in later stages. The endarteritis occludes the blood supply to the skin and is responsible for the ulcer of the chancre and the gumma. In secondary syphilis, there is endothelial swelling in the vessels that is associated with a sleeve of plasma cells. In late syphilis, epithelioid cells, fibroblasts and giant cells are found in the skin in addition to the vascular changes and plasma cells.

Immunohistochemistry shows a predominantly $CD8^+$ lymphocyte infiltrate. Warthin–Starry staining may demonstrate the spirochaetes. A specific immunostain for *T. pallidum* is becoming available.

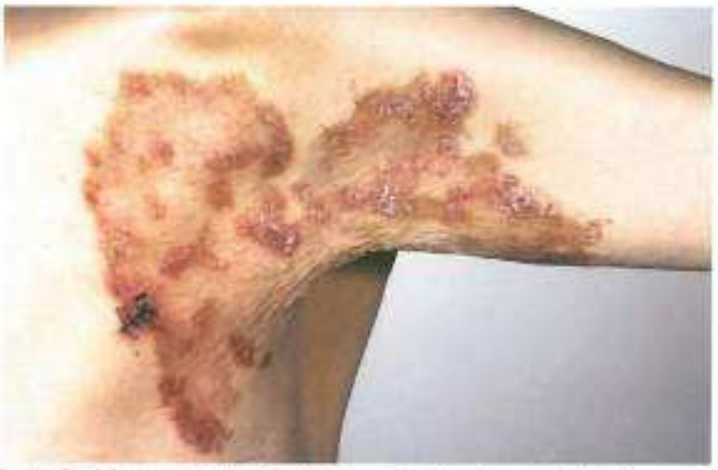


Fig. 13.73 Tertiary syphilis. The lesions are annular and consist of red-brown papules and infiltrated scaling plaques within the lesion. The diagnosis was suggested by an astute dermatologist and confirmed by a skin biopsy. (Courtesy of Dr Andrew Pembroke.)

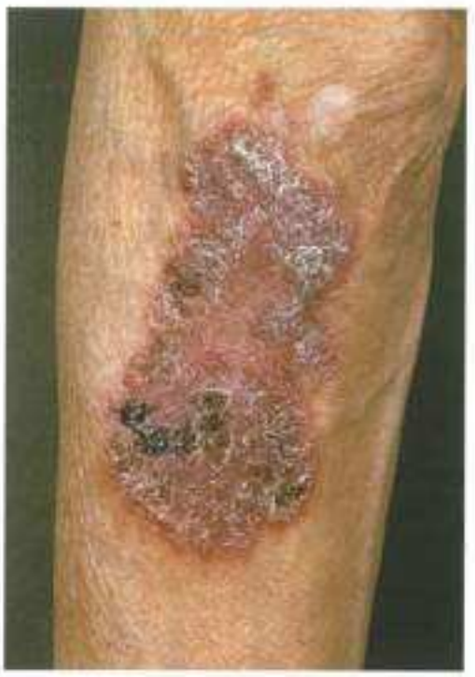


Fig. 13.74 Tertiary syphilis. This scaly plaque could well have passed for psoriasis, but the solitary nature of the lesion raised the possibility of syphilis which is the great mimic of many skin disorders.

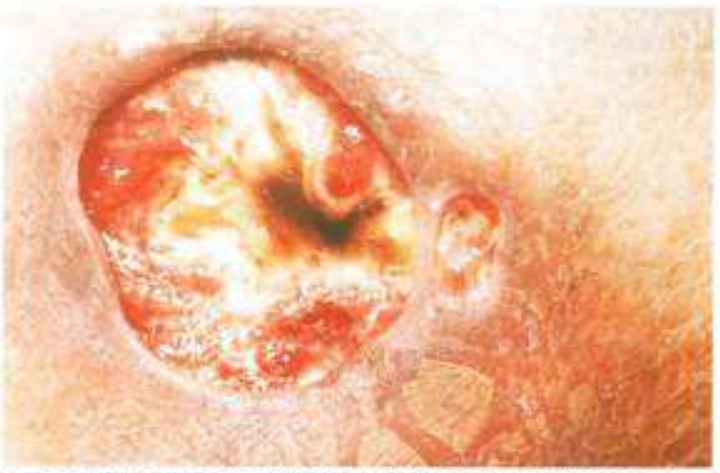


Fig. 13.75 Tertiary syphilis. The ulcer is well defined with vertical edges and appears 'punched-out'. The base has a yellow slough. (Courtesy of St Mary's Hospital.)

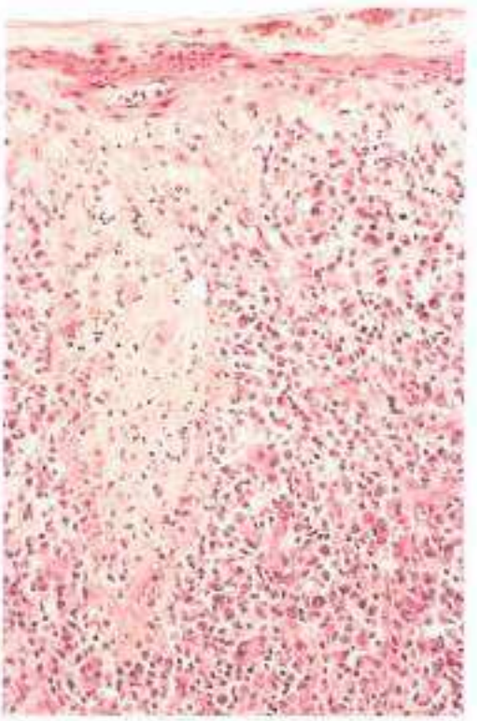


Fig. 13.76 Syphilis. The dermis contains a heavy, chronic cell infiltrate with numerous plasma cells. The epidermis contains large numbers of neutrophils.

Management of Syphilis

The spirochaetes are usually identifiable by dark-field microscopic examination in the primary and often in the secondary stages. Skin biopsy may be helpful in undiagnosed eruptions. Serological tests are positive by the second stage. The venereal diseases reference laboratory test (VDRL) and the rapid plasma reagin test (RPR) are the most widely used. These identify antibodies to cardiolipin, a component of the mammalian cell, which is modified by treponemes such that antibodies result in an infected patient. Antibodies to surface proteins of *T. pallidum* can be detected by haemagglutinin antibodies. They may be positive for life and include the TPHA (*T. pallidum* haemabsorption test), MHA-TP (microhaemagglutination assay for antibodies to *T. pallidum*) and FTA-ABS (fluorescent treponemal antibody absorption assay). Intramuscular long-acting high dose (2.4 million units) benzylpenicillin (penicillin G) is still the treatment of choice. For those allergic to penicillin, azithromycin or tetracycline are second line drugs.

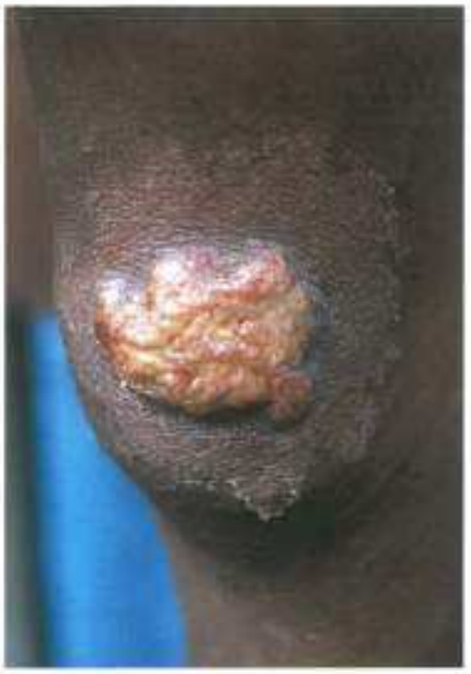


Fig. 13.77 Yaws. This is early yaws or 'mother' lesion. The yellow crusted lesion is highly infectious. (Courtesy of Drs H.J.H. Engelkens and E. Stolz, Rotterdam.)

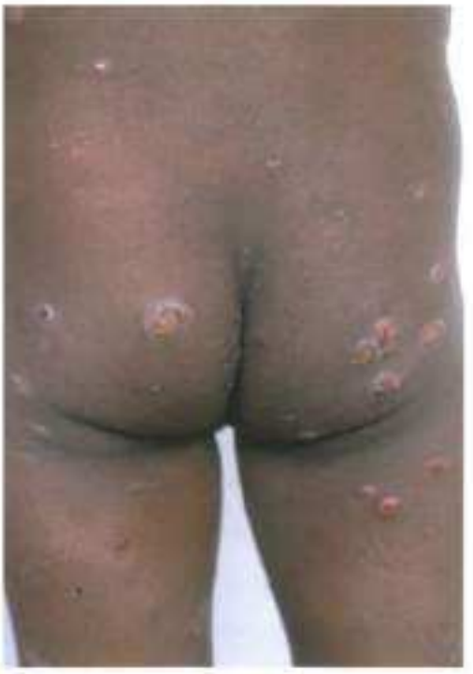


Fig. 13.78 Yaws. Eroded areas teeming with spirochaetes are typical of 'daughter' yaws. (Courtesy of Drs H.J.H. Engelkens and E. Stolz, Rotterdam.)

Yaws

A contagious but non-venereal treponematosis caused by *T. pallidum* subspecies *pertenue*.

Aetiology

Yaws occurs in children in areas of heavy rainfall and temperatures above 27°C, which include Africa, Asia, South and Central America and the Pacific Islands. It is spread from mucous membrane or skin contact and via fomites. There seems to be no difference between the subtypes of *T. pallidum* with Western blotting, Southern hybridization and immunoblotting techniques, but a study has suggested that there is a single nucleotide difference between yaws and syphilis, with guanine substituting in yaws for an adenine in syphilis. Like syphilis, yaws has primary, secondary and tertiary stages.

PRIMARY (MOTHER) YAWS

Clinical Features

Symptoms

A sore appears 9–90 days after inoculation of damaged, exposed skin.

Morphology

An erythematous indurated papule enlarges and may become confluent with satellite lesions (Fig. 13.77). They ulcerate with an amber, yellow crust. The red, rather pulpy surface of the ulcer resembles a raspberry. It is highly infectious and subsequently heals with a hypopigmented scar.

Distribution

The papule occurs at the point of contact (usually buttocks, lower limbs or mucous membranes).

Systemic signs

There is usually fever, joint pains and lymphadenopathy.

SECONDARY YAWS

Clinical Features

Symptoms

The patient is unwell with a headache, fever, malaise and bone and joint pains.

Morphology and distribution

There are various forms of rash, partly depending on the distribution:

- a widespread morbilliform eruption
- 'daughter' yaws: expanding ulcerations teeming with spirochaetes; these occur particularly around body orifices (the mouth and nose)
- 'linea yaws': some lesions coalesce or heal centrally, producing circinate lesions
- condylomatous lesions in the axillae and groin
- palmo-plantar lesions: simulate secondary syphilis and, occasionally are hyperkeratotic and painful such that the patient has a crab-like gait.

All the lesions heal without scarring but relapses are common, particularly around the anus, in the axillae and in the mouth.

Systemic

The bones and joints are painful, with an osteoperiostitis and polydactylitis affecting the hands, forearms, feet and legs.

TERTIARY YAWS

Clinical Features

Symptoms

Just like in syphilis, a non-infectious latent period follows the initial infection and then about 10% of patients develop a tertiary stage comprising abscesses and ulcers of the skin (Fig. 13.78) and thickening of the palms and soles.

Morphology and distribution

Subcutaneous nodules develop into deeply destructive and deforming abscesses or ulcers (Fig. 13.79). Squamous cell carcinoma may ultimately develop. In addition, there is a keratoderma of the palms and soles.

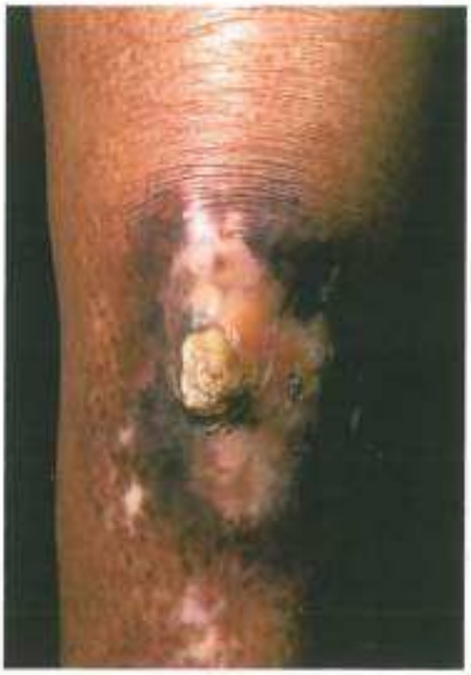


Fig. 13.79 Yaws. Nodules, abscesses and ulcers develop in the tertiary stage. Squamous cell carcinoma may result. There may be osteomyelitis of the bones (particularly the tibia) and joints.

Systemic

The bones and joints are involved. There is a hypertrophic gummatous periostitis with osteitis and osteomyelitis. A sabre-like appearance occurs on the shins. The nose may be involved, with septal and bony destruction.

Management of Yaws

The diagnosis of yaws is made by finding treponemes on dark-field examination. The serological reactions to syphilis are positive (the specific treponemal immobilization test and non-specific floculation and complement fixation tests). Yaws responds to penicillin and was nearly eradicated by a World Health Organization campaign in the 1960s, but there has been some resurgence. Better living conditions and the use of soap and water for washing have also accounted for its decline.

BEJEL (ENDEMIC) YAWS

Bejel (endemic) yaws is a non-venereal treponematosis particularly affecting children living in primitive overcrowded conditions; it simulates the secondary stages of syphilis, with often undetected primary stages.

Aetiology

It is caused by *T. pallidum endemicum*. It affects children who have close skin contact but it is also spread by fomites. It is seen in the dry and desert areas of Arabia and in the Sahara and particularly affects semi-nomads and the Bedouins.

Clinical Features

Primary stage This is rare, probably because there is a less heavy primary inoculation than in venereal syphilis. However, there may be an oropharyngeal mucosal chancre from the nipple of a nursing mother.

Secondary stage The child may be unwell with lymphadenopathy, hoarseness from oral lesions and osteoperiostitis, causing nocturnal leg pains as in yaws.

Morphology and distribution

- Condylomas in the axillae and anogenital area are common
- There is a non-pruritic disseminated papular eruption
- There may be an angular stomatitis and mucous patches in the mouth and throat.

Systemic

Tertiary stage gummas are not common but affect the nasopharynx, larynx and skin. The palate and nasal septum may be involved, affecting swallowing and articulation. There may be bony destruction and involvement of the tibia. Cardiovascular and neurological involvement is rare.

Management

Serological tests for syphilis are positive and the condition responds to penicillin.

Pinta

Pinta is a *T. carateum* infection of the skin, occurring in the Western hemisphere. It spreads between family members, causing a dyschromic skin eruption and hyperkeratosis.

Aetiology

Pinta means spotted (Spanish, to paint). It occurs in primitive, unhygienic communities in South and Central America and Mexico through direct skin or mucous membrane contact, usually in childhood. There is no lifelong immunity and the disease is contagious for protracted periods; it is harboured by patients with subclinical or mild disease.

Clinical Features

Symptoms

Begins at the site of inoculation with a small spot. In the secondary stage, there are sparse or numerous patches of varied colour, which in the third stage are depigmented and mottled, simulating vitiligo (Fig. 13.80).

Morphology and distribution

70 days after inoculation a minute papule surrounded by a red halo occurs. It grows by direct extension or fusion with satellites to produce a lesion up to 10 cm in diameter, usually on the lower leg.

In the secondary infectious stage (a month or years later), a few or many small scaly papules coalesce to form psoriasiform plaques, which may be violaceous slate-blue, brown or grey-black. They intermix and fade. It relapses producing oval polycyclic configurations.

In the tertiary pseudovitiliginous non-infectious stage, the lesions are depigmented and mottled. There may be atrophy and hyperkeratosis.

Management

Serological tests are positive and it responds to penicillin or tetracycline.

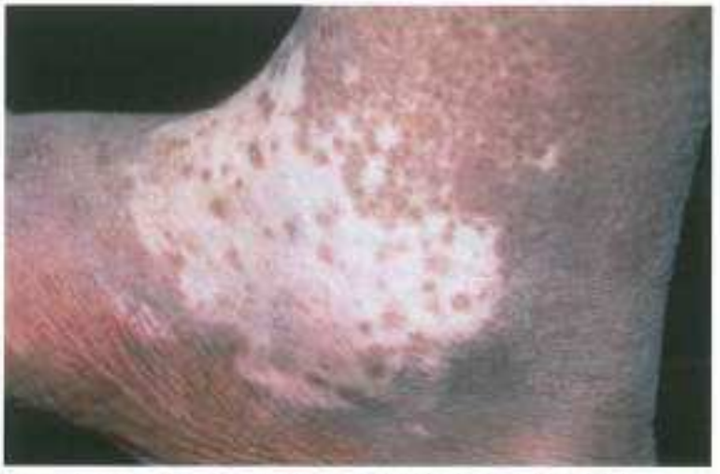


Fig. 13.80 Pinta. In late disease there is a hyperpigmented border (right) surrounding pseudovitiligo. (Courtesy of Drs R. Arenas and J. Salas, Guadalupe.)

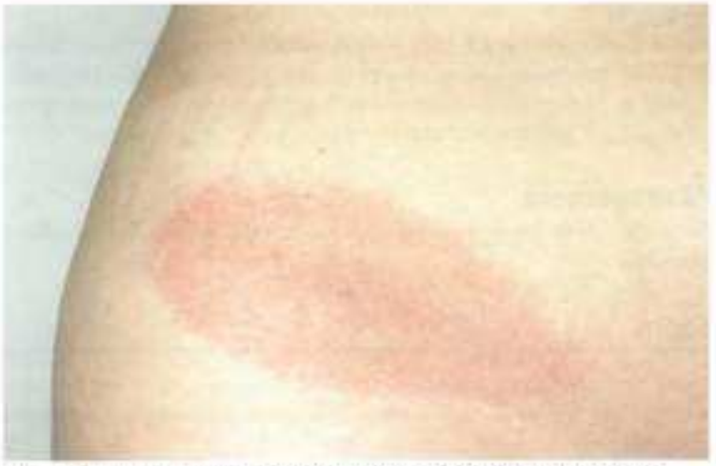


Fig. 13.81 Lyme disease. The annular erythema is also known as erythema migrans chronicum.

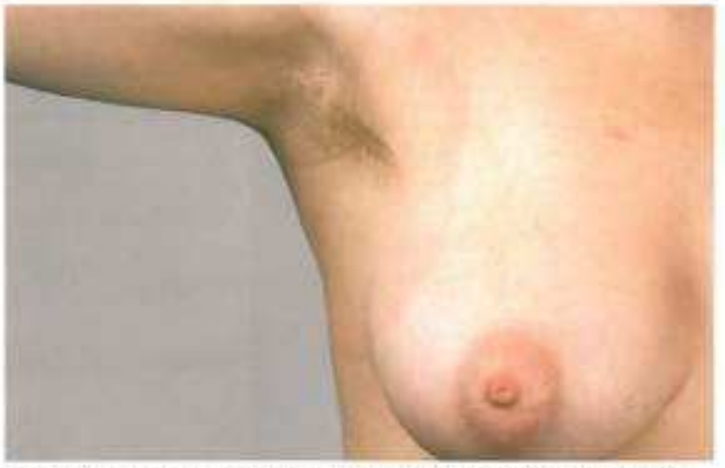


Fig. 13.82 Lyme disease. The annular configuration is clearly delineated. The rash spreads outwards from the site of the bite.

Lyme disease

A disorder with potential joint and neurological sequelae that is initially introduced to the skin via a bite from a tick infected with the spirochaete *Borrelia burgdorferi* from an animal reservoir.

Aetiology

The disease is named after Lyme, a town in Connecticut where the original outbreak of seronegative arthritis was described in 1975. However, the rash (erythema chronicum migrans) and the neurological symptoms that followed it or the tick bite had been known in Europe since the early part of the 20th century. A new spirochaete was isolated from *Ixodes dammini* ticks by Burgdorfer in 1982 and was named *B. burgdorferi*. It was subsequently isolated from the skin, blood and cerebrospinal fluid of patients with Lyme disease. The white-footed mouse is the main reservoir of infection in the USA, but squirrels and other mammals may carry it in wooded regions such as the New Forest in the UK. Deer are then affected and are the main host; cattle and sheep may also be affected. There may be different strains of *B. burgdorferi*. In the USA, multiple cutaneous lesions, the early disseminated stage, arthritis and post-Lyme fatigue are much more common than in Europe. By comparison, borrelial lymphocytoma near or at the site of the original bite, acrodermatitis chronica atrophicans and encephalitis are reported more commonly in Europe.

Clinical Features

Symptoms

A rash occurs 3 to 30 days (occasionally 3 months) after a tick bite.

Morphology

Stage 1 (early localized borreliosis) A self-limiting erythema gradually spreads outwards from the site of the bite (Figs 13.81 and 13.82).

Stage 2 (early disseminated borreliosis) Headache, malaise, chills, myalgia, lymphadenopathy and generalized arthralgia develop, lasting several weeks; these may be followed by neurological manifestations of a triad of cranial polyneuropathy, a painful radiculopathy and chronic meningitis. The cranial nerve most involved is the 7th and there is either unilateral or bilateral lower motor neurone facial palsy. There may be carditis (including heart block) and polyarthralgia.

Stage 3 (late persistent borreliosis) A chronic asymmetrical oligoarthritis affecting the large joints, sometimes accompanied by malaise and depression, has been described in the USA although rarely in the UK.

Acrodermatitis chronica atrophicans is a diffuse or localized oedema and erythema of extensor surfaces including the hands, feet, elbows and knees, which gradually becomes atrophic. It is rare in the USA but is reported in Europe.

Lymphadenosis benigna cutis is a borrelia lymphocytoma that occurs as a solitary bluish red nodule or plaque as a late cutaneous complication. Encephalomyelitis may occur in the late persistent stage.

Management

The history of a tick bite and the characteristic skin eruption allow the diagnosis to be made clinically. Serologically, enzyme-linked immunosorbent assays (ELISA) for antigen-specific IgM are unreliable but may be positive after 3 weeks, diminish at 6 weeks and be followed by a rise in the IgG titre. The organism may be cultured from a skin biopsy and PCR may be used to amplify *B. burgdorferi* DNA. Patients with chronic meningitis have positive antibody titres in cerebrospinal fluid or serum.

Oral tetracycline or penicillin are effective treatments for erythema migrans and seem to shorten the course of the rash and reduce the chance of complications. Doxycycline 100 mg three times a day for 21 days or amoxicillin 1 g plus probenecid 500 mg three times a day for 21 days and cefuroxime axetil 500 mg twice daily for 21 days are all regimens that have been reported as being successful.

Chancroid

Chancroid is a venereal infection caused by *Haemophilus ducreyi*.

Aetiology

It is common in societies with poor social and hygienic standards in Africa, the Far East, Central and South America. It particularly affects males who frequent prostitutes. It is a risk factor for spreading HIV.

Clinical Features

Symptoms

A painful genital sore appears 2–5 days after infection, with tender inguinal lymph nodes that may suppurate.

Morphology

The small red papule rapidly becomes a pustule, which then ulcerates. It is round or oval, has a ragged undermined edge and is surrounded by a red

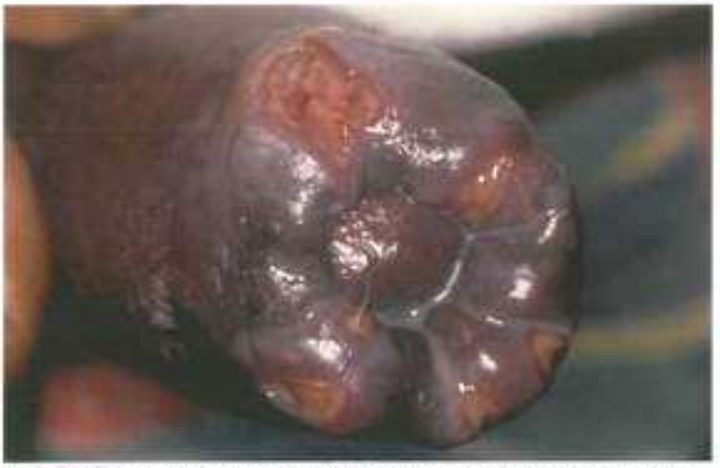


Fig. 13.83 Chancroid. The initial red papule breaks down to produce an ulcer with a ragged undermined edge that enlarges, producing several satellite ulcers. (Courtesy of Dr David A. Lewis.)

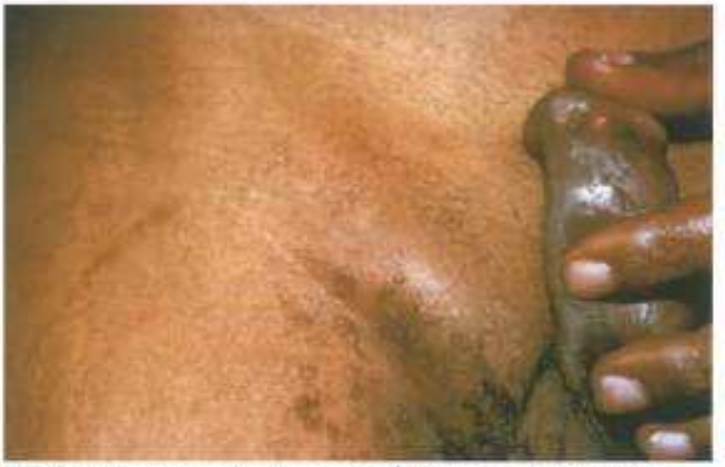


Fig. 13.84 Lymphogranuloma venereum. A sore is present on the corona, which is followed by a painful, unilateral bubo visible in the groin. (Courtesy of Dr David A. Lewis.)

very vascular areola (Fig. 13.83). It enlarges slowly to produce satellite ulcers, often up to five in number.

Distribution

The lesions occur on the genitalia (rarely elsewhere). There is an inguinal adenitis in most cases, which is tender and which may suppurate (bubo). Males are usually uncircumcised. Females may have multiple, often asymptomatic lesions in the introitus, on the cervix or in the perianal region.

Management

H. ducreyi may be identified as chains of coccobacilli in smears from the ulcer or from the pus of a bubo or a culture. Tests for other venereal diseases should be performed. It must be distinguished from a syphilitic chancre but the latter is not painful. A 7 day course of erythromycin or a single dose of azithromycin (1 g orally), or ceftriazone (250 mg intramuscularly) is usually successful. Ciprofloxacin (500 mg b.d.) is also effective, but is contraindicated in pregnancy.

Lymphogranuloma venereum (Lymphogranuloma inguinale)

A tropical venereal disorder caused by *Chlamydia trachomatis*.

Aetiology

C. trachomatis is an obligate, intracellular parasite that has a cell wall in its infectious form. It contains RNA and DNA. There are two chlamydial subgroups, one contains *C. trachomatis* and the other *C. psittaci* (which is endemic in birds and occasionally causes psittacosis). *C. trachomatis* has various serotypes: A, B and C cause trachoma, D to K cause urethritis and deeper pelvic infections and L1–3 involve lymphatic tissue and cause the sexually transmitted disease of lymphogranuloma venereum. It is endemic in Africa, Asia and the Caribbean.

Clinical Features

Symptoms

After an incubation period of 10 days, a sore appears on the genitals, which heals rapidly. A week or month later a painful, often unilateral, bubo (Fig. 13.84) in the groin follows and the patient may be unwell.

Morphology and distribution

A papule or small vesicle appears on the genitalia (occasionally elsewhere), which may be inconspicuous, and heals rapidly. The inguinal glands are swollen and remain so for some weeks.

Systemic

There are constitutional features of malaise, joint pains and stiffness, hepatosplenomegaly and sometimes photosensitivity and erythema nodosum. There are various sequelae if the patient is untreated.

The condition can resolve completely or develop into an inguinal syndrome of hard tender glands, which become matted and subsequently break down forming sinuses draining through a red/purple skin.

In females, a rectal syndrome may develop if the primary lesion was in the vagina. The pelvic glands become enlarged and there is a periproctitis and proctitis, which may develop into a rectal stricture and fistulae. Carcinoma may develop subsequently.

A genital syndrome occurs in both sexes in which there is genital lymphoedema leading to elephantiasis, which in females is known as esthiomene, being combined with scarring and fistulae of the buttocks and thighs. In males a 'saxophone' penis develops from the lymphoedema with the strictures and fistulae.

An anorectal syndrome of proctitis or protocolitis is increasingly being recognized in Europe, particularly in homosexual males with anonymous partners in association with HIV and hepatitis C.

Management

The diagnosis is made by complement fixation tests which, however, cross-react serologically with respiratory *Chlamydia* and therefore only detect the genus. New serological techniques beset on micro-immunofluorescence can identify the serovar. Aspiration of the bubo may be necessary. Other causes of venereal diseases should be excluded. Although lymphogranuloma venereum is best treated with tetracyclines, 500 mg four times daily for 14 days, if there is concomitant *H. ducreyi* infection, erythromycin, doxycycline or azithromycin should be given instead. Early treatment is important to prevent the sequelae of lymphatic obstruction.

Granuloma inguinale (Donovanosis)

A chronic granulomatous infection of the genitalia and surrounding skin caused by *Calymmatobacterium* (formerly *Donovania*) *granulomatis*.

Aetiology

C. granulomatis is a small pleomorphic non-motile Gram-negative bacteria exhibiting bipolar staining. It is a fastidious organism but can be isolated on the yolk sac of the chick embryo. It may be seen in large mononuclear cells as Donovan bodies using Wright's stain of cytological preparations (Fig. 13.85). It is endemic in the tropics and sub-tropics.

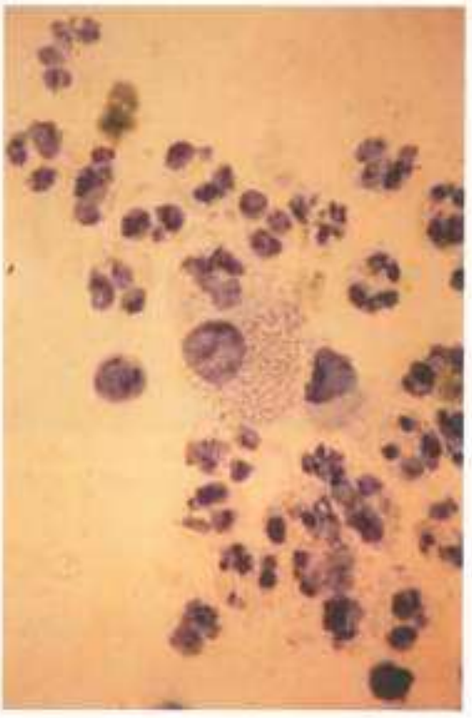


Fig. 13.85 Donovan bodies. Giemsa staining of a smear from the ulcer shows intracellular encapsulated bacteria within large mononuclear cells. (Courtesy of Dr David A. Lewis.)

Clinical Features

After an incubation of 9 to 50 days, a non-painful genital sore occurs without adenitis.

Morphology

There is a firm papule or nodule that breaks down to form an ulcer with a sharply defined overhanging edge. The subsequent course depends on the degree of healing, destruction and epithelial hyperplasia (Fig. 13.86). There may be a deep and rapid ulceration (Fig. 13.87) especially in women, which extends into the groins and other flexures, often with vegetative changes. It may resolve or it may extend intermittently and irregularly for years with secondary infection, leading ultimately to cachexia with possible spread to the liver, spleen and bones. The patient may die.

Management

Smears should be taken from the edge of the lesion for Donovan bodies. Histologically, there is an inflammatory reaction of plasma cells and polymorphs in the skin and subcutis, with large mononuclear cells containing Donovan bodies. Tetracyclines are effective, as are erythromycin, streptomycin, chloramphenicol and gentamycin. The last is being used in those with widespread disease.

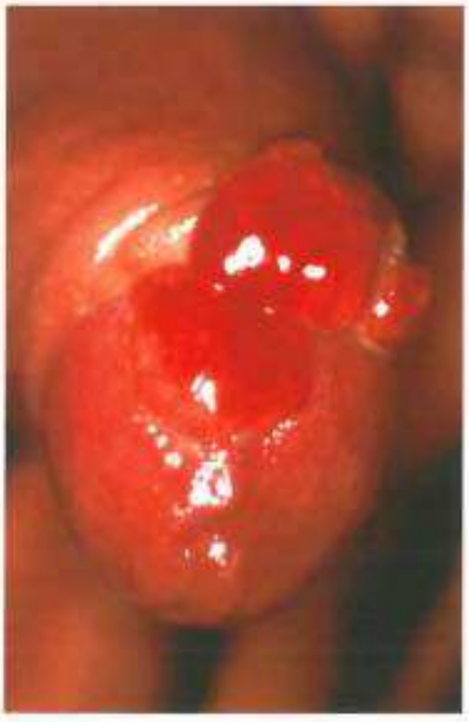


Fig. 13.86 Donovanosis. In granuloma inguinale, there is a beefy red, raw ulcer with a sharply defined margin; a polypoid mass of granulation tissue occurs with healing. (Courtesy of Dr David A. Lewis.)

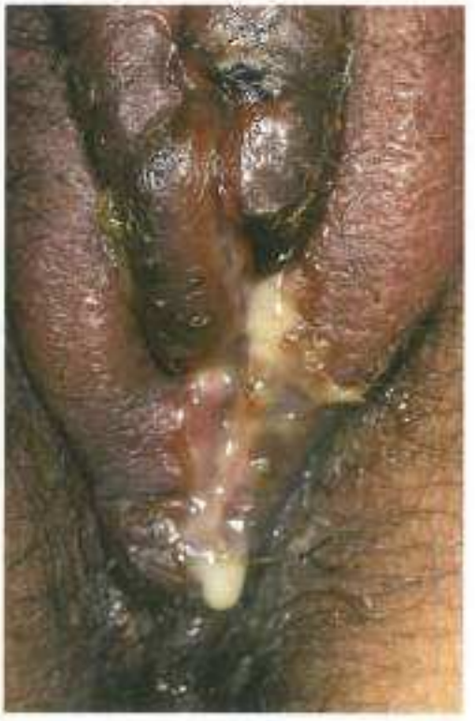


Fig. 13.87 Donovanosis. The initial firm papule breaks down into an ulcer with a sharply defined, overhanging edge. Deep extensive ulceration may follow quite rapidly. A foul-smelling exudate is characteristic. (Courtesy of Dr E. Higgins.)

Rocky Mountain spotted fever

A vasculitis affecting the skin and nervous system secondary to a bite from a tick infected with *Rickettsia* sp.

Aetiology

Rickettsia are small Gram-negative bacteria that are mostly obligate intracellular parasites. They are transmitted by blood-sucking arthropods and infect endothelial cells where they are phagocytosed by host cells, in which they multiply and accumulate, causing cell lysis. This causes infarcts, disseminated intravascular coagulation and extravascular fluid loss, resulting in hypotension and shock. Rocky Mountain spotted fever is transmitted by the hard ticks of *Dermacentor* sp. and is endemic in Maryland, Virginia and North Carolina on the east coast of the USA (*D. variabilis*), in certain countries in Central and South America and the Rocky Mountain states (*D. Andersoni*) of North America. It is most common between April and September and worse in G6PD-deficient subjects. Dogs act as a mammalian reservoir for the disease. About 19 species of *Rickettsiae* have been identified.

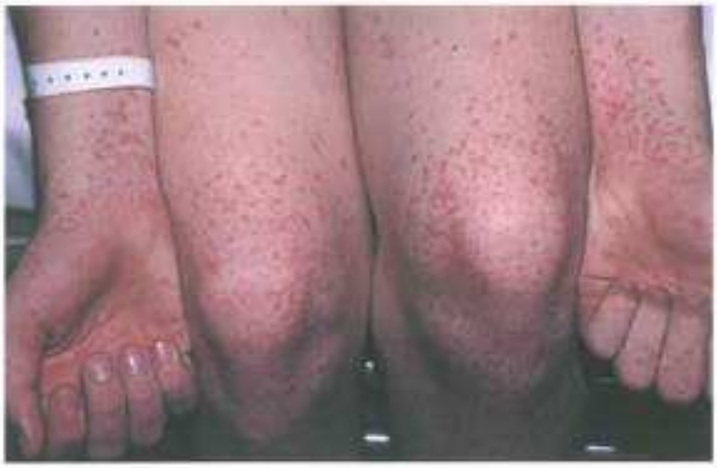


Fig. 13.88 Rocky Mountain spotted fever. The petechiae move centripetally from wrists, palms and legs to the trunk. (Courtesy of Dr J. Calen.)

Clinical Features

The patient has a fever of up to 40°C, malaise and headache, which is followed by a rash between days 3–6. There may be a history of a tick bite, especially on the head, neck or shoulder.

Morphology

There are erythematous macules that become palpable and purpuric (Fig. 13.88) within a few hours. If untreated, large ecchymoses are followed by massive skin necrosis. An eschar at the site of the tick bite is rarely seen, unlike in other rickettsial infections such as tick and scrub typhus.

Distribution

The eruption moves centripetally from the wrists, ankles, palms and soles to the trunk and the face. Acral gangrene may occur in severe infections.

Systemic features

High fever, severe headache, myalgia, non-productive cough, nausea, vomiting and abdominal pain.

Management

This is a serious disorder with a mortality of 20% without treatment. Tetracyclines should be started immediately the diagnosis is suspected. General supportive measures are indicated.

The diagnosis is made using serological techniques but this takes weeks. Skin biopsy shows a small vessel vasculitis characterized by mononuclear leucocyte infiltration following the invasion of the rickettsia into the endothelial cells. Direct immunofluorescence staining for the rickettsial antigens may be positive. There may be leucopenia, thrombocytopenia, hyponatraemia and a raised aminotransferase.

Other rickettsia produce rashes (but not Q fever).

Epidemic typhus caused by *R. prowazeki* is similar but the trunk and axillary folds are affected first and the eruption then spreads centrifugally; the palms, soles and feet are usually spared although acral gangrene of the fingers, toes, scrotum and nose may occur in severe infections. The face is often flushed with conjunctival injection. It is transmitted by lice in catastrophic situations (war, earthquakes, etc.) and has an incubation period of 1 or 2 weeks. Recovery depends on the speed of treatment and how seriously the central nervous system and myocardium are involved.

Scrub typhus caused by *R. (Orientia) tsutsugamushi* is transmitted by mites that naturally infect rodents. The eschar from the primary bite is usually visible and there is generalized lymphadenopathy, maculopapular generalized rash, pneumonitis and myocarditis. It occurs in the Far East and southwest Pacific.

Tick typhus (Mediterranean fever, fièvre boutonneuse) is transmitted by an ixodid tick infected with *Rickettsia* sp. (e.g. *R. conori* and *R. australis*) and is endemic in Africa, India and countries bordering the Mediterranean. An eschar develops at the site of the bite and coincides with a fever, general constitutional disturbance and a maculopapular rash, which may become haemorrhagic.

Meningococcaemia

A purpuric rash, septicaemia and meningitis caused by *Neisseria meningitidis*.

Aetiology

N. meningitidis is an obligate aerobic Gram-negative kidney-bean-shaped coccus that is seen in pairs with the long axes parallel. These are known as diplococci. The infection enters the upper respiratory tract via droplets from an infected patient or healthy nasopharyngeal carrier (40% adults). The condition is most common in crowded conditions, for example schools and universities. The diplococci penetrate the epithelial walls and result in a neutrophilic vasculitis and subsequently disseminated intravascular coagulation with extensive necrosis of blood vessels and thrombosis. Meningococcaemia is prevalent in crowded institutions and common in congenital or acquired complement (especially C5 to C8), properdin or immunoglobulin deficiency and asplenia. Meningococcaemia occurs sporadically in industrialized countries, but is a major disease burden in non-industrialized countries. Infants and young adults are most vulnerable. Infection is classified by its polysaccharide capsule. A is common in Africa, B and C in the West, W-135, X in Africa and Y in the USA. Group B is the predominant isolate in developing countries.

Clinical Features

Symptoms

Following a mild upper respiratory tract infection, there may be headache, nausea, vomiting and muscle soreness or the condition may proceed very rapidly from fever to obtundation with stupor, haemorrhagic rash,

hypotension and shock with disseminated intravascular coagulation and the Waterhouse–Friderichsen syndrome (adrenal shutdown) within hours.

Morphology

Classically, the rash is purpuric and haemorrhagic but not always. It begins as discrete pink macules or papules that are a few millimetres in diameter. They are often small and stellate in shape (Fig. 13.89), rather grey-purple in colour and may be tender. They have a somewhat irregular and 'smudged' appearance. They sometimes have a vesicular or pustular centre. Purpura fulminans, an ominous sign, results in untreated or rapidly progressing disease (Fig. 13.90). There are extensive bullous and haemorrhagic lesions with central necrosis resulting in gangrene (Fig. 13.91).

Distribution

The rash can occur anywhere but particularly on the lower extremities and trunk, also on the palms and soles, upper body, face, head and mucous membranes including the conjunctivae. It may, however, be quite sparse. Extensive ecchymoses, necrosis and ulceration occur quickly on pressure areas and dependent and acral sites.

Management

The diagnosis is clinical, and treatment should be started immediately the diagnosis is suspected. The histology does show a leucocytoclastic vasculitis with intraluminal thrombi. Gram-negative cocci are seen in the endothelial walls and in the neutrophilic infiltrate. Gram stains of the skin often reveal the bacteria. Blood cultures are positive in the majority. Bacteria are also found in the cerebrospinal fluid.

Penicillin (2 million units) should be given intravenously every 2 hours until approximately 7 days after the temperature returns to normal in adults.

Meningococcaemia is a disorder of children and young adults. Vaccines are available but not for diplococci with group B capsular polysaccharides.

Chronic meningococcaemia does occur. These patients develop erythematous, tender papules and nodules with a haemorrhagic centre. The lesions may be pustular or vesicular but they are usually less than a centimetre in diameter. The trunk, extremities and the skin of overlying joints are involved. The patient has an intermittent fever and joint involvement. The diagnosis is made on blood cultures or by PCR of DNA extracted from lesional skin. Treatment is with penicillin or with a third-generation cephalosporin if the organism is penicillin resistant.

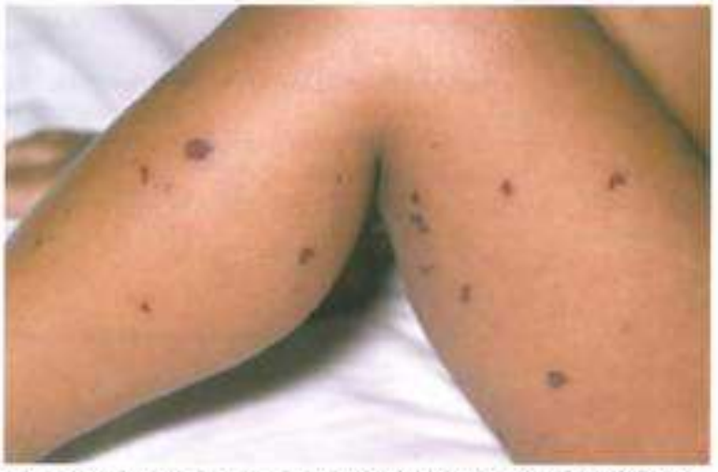


Fig. 13.89 Meningococcaemia. Purpuric stellate macules are scattered on the limbs in this 2-year-old child. (Courtesy of Dr Georgiana Vergani.)

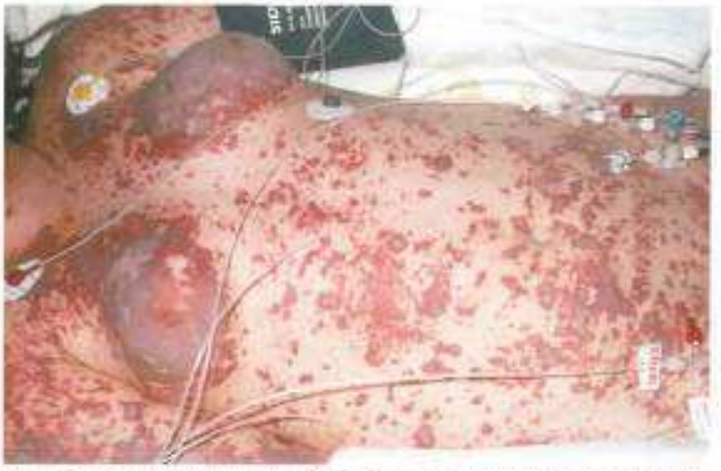


Fig. 13.90 Meningococcaemia. There is widespread purpura that has become 'fulminans' over the breasts. It is an ominous sign.

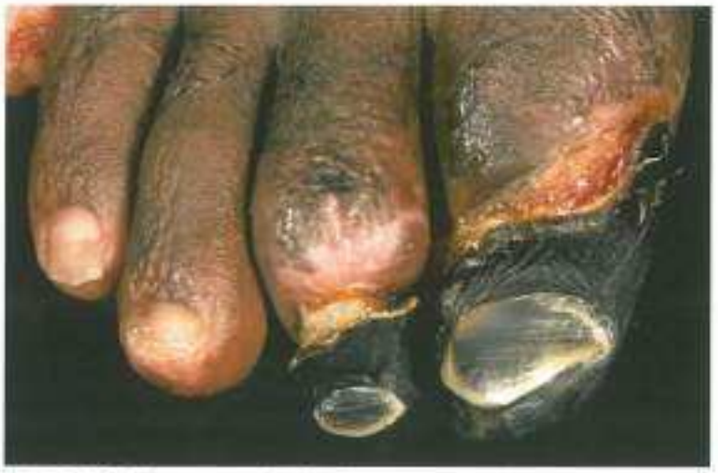


Fig. 13.91 Meningococcaemia. Acral gangrene occurs in severe meningococcal septicaemia, with disseminated intravascular coagulation.

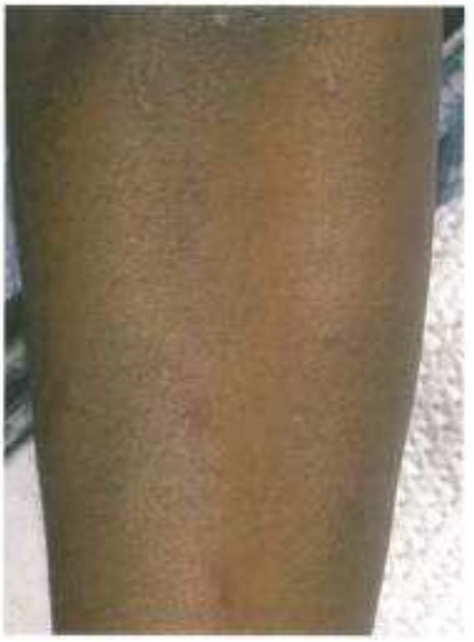


Fig. 13.92 Gonococcaemia. There are scattered papulopustules in this young male, who has a fever and an oligoarthralgia.

Gonococcaemia

A disseminated infection with *Neisseria gonorrhoeae*, which causes fever, arthritis and a characteristic acral papulovesicular eruption.

Aetiology

Gonorrhoea is caused by a Gram-negative diplococcus and is usually diagnosed in its primary stage as an urethral, anal or vaginal discharge; however, in females the discharge may be minimal or not noticed, in which case gonococcaemia may result, particularly if contracted during menstruation. In addition, the responsible organism appears to be slightly different from that which causes gonorrhoea limited to the mucous membranes. Patients with C5–C9 deficiencies of complement are at risk.

Clinical Features

Symptoms

The patient is usually a young adult female who is unwell, has a fever and an arthritis involving one or several joints, especially the knee, wrist and ankle.

Morphology

Discrete haemorrhagic vesiculopustules surrounded by erythema.

Distribution

They occur on the extremities (Fig. 13.92), especially the fingers (Fig. 13.93), palms, toes and soles.

Management

The diagnosis may be established by Gram staining and culture of the organism from swabs taken from the urethra, vagina and anus. DNA hybridization tests are efficient but do not permit antibiotic sensitivity testing. Swabs from the lesions themselves are usually negative for gonococci, but the histology does show a vasculitis and immunofluorescence is positive for *N. gonorrhoeae*. Third generation cephalosporins are the treatment of choice as penicillin, tetracycline, erythromycin and quinolone resistance have become commonplace.

Leptospirosis

An infection caused by the *Leptospira* complex of organisms, often transmitted by rodents.

Aetiology

It is transmitted by mammals who excrete the organism in their urine. Those who work in sewers or handle animals are at risk. Occasionally, it is contracted from swimming or fishing in contaminated water. The portal of entry into the human is usually via the gut but may be via an abrasion.

Clinical Features

Symptoms

There is an incubation period of 1–2 weeks followed by an acute illness with fever, muscle pains and headache. The conjunctivae are injected. There may be respiratory symptoms and jaundice with purpura (leptospirosis ictero-haemorrhagica, *Weil's disease*).

Morphology

Purpura or a non-specific blotchy erythema is associated with petechiae.

Distribution

The blotchy erythema may be widespread (Fig. 13.94) or tender macules and papules may be limited to the shins.

Management

The diagnosis is established by isolating the organism from the blood or by a substantial rise in serological titres. Either penicillin or doxycycline is the treatment of choice.

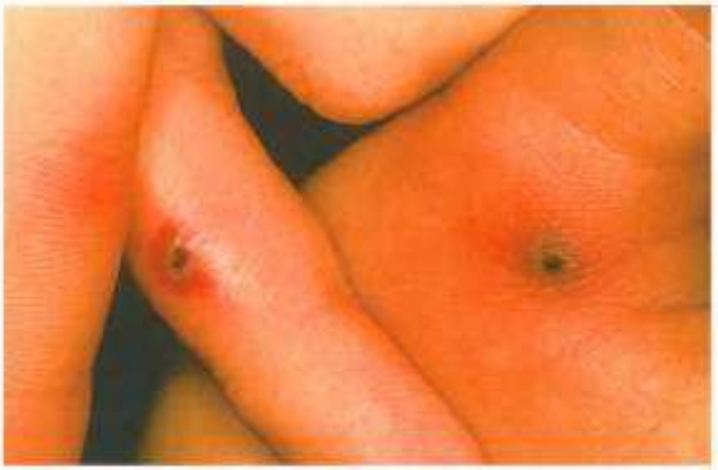


Fig. 13.93 Gonococcaemia. The lesions are haemorrhagic pustules on an erythematous base. (Courtesy of Dr Frank Dann, Los Angeles.)

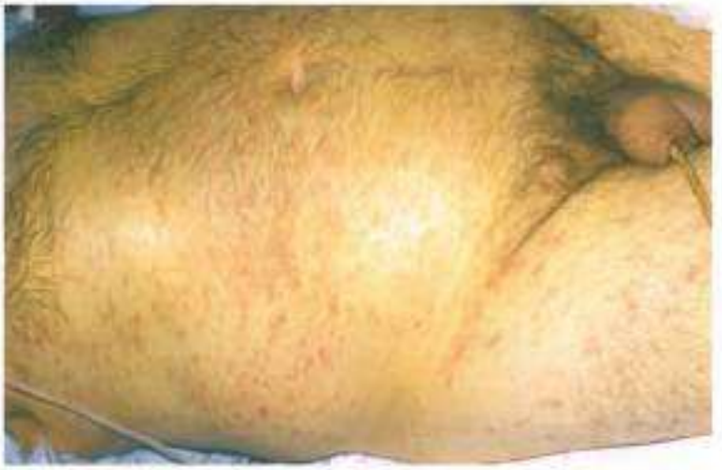


Fig. 13.94 Leptospirosis. There is a non-specific, blotchy erythema in addition to jaundice.

Anthrax

Caused by *Bacillus anthracis*, this is primarily an infection of herbivores, which infects man either directly from animals or their products via ingestion, inhalation or inoculation of spores. These grow rapidly to produce organisms which release toxins.

Aetiology

Bacillus anthracis is a Gram-positive encapsulated aerobic or facultative anaerobic non-motile spore-forming bacillus which can survive for many years as spores in the soil. Animals become infected by ingesting the spores. This is a problem in Africa, the Middle East, Latin America, the Indian sub-continent and parts of Russia. Humans who work with wool, hair, bristle or animal imports from the above countries or unsterilized bonemeal are at risk. Normally human resistance is high but spores may be inoculated via minor trauma or inhaled into the lungs or ingested into the intestine before proceeding to the blood. Humans are also at risk from biological warfare, or accidental escape and windborne spread of spores from biological weapons factories (e.g. Sverdlovsk in 1979), causing cutaneous, inhalational or gastrointestinal anthrax.

Clinical features

Symptoms

Cutaneous anthrax presents as a sore usually on an exposed site.

Morphology

The *malignant pustule* commences as an itchy painless papule one to five days after exposure and develops into a bulla on a red oedematous base. The blister becomes a haemorrhagic crust (Fig. 13.95) around which there is a zone of redness and oedema, which may be surmounted by several small vesicles. This is followed by an ulcer with a black eschar. The inoculum may spread to the eyes, face and neck causing oedema (malignant oedema).

Distribution

A site easily exposed to inoculation.

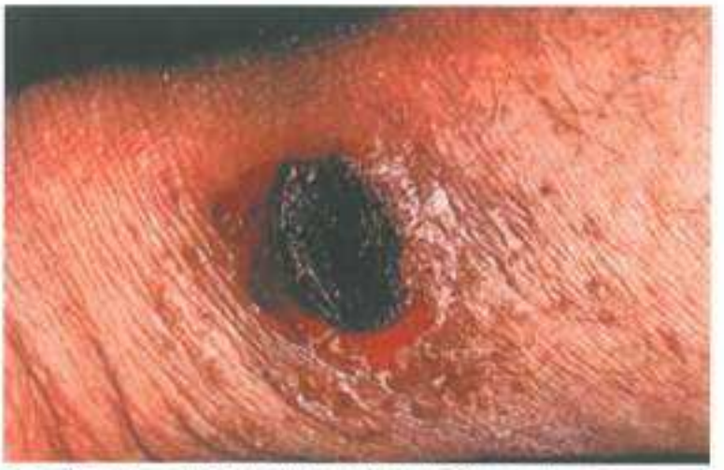


Fig. 13.95 Anthrax. This is the '*malignant pustule*'. There is a haemorrhagic crust surrounded by a zone of erythema and oedema. (Reprinted from Infectious Diseases, 3rd Edition, Edmond, Rowland and Wessby, p153, 1995, by permission of the publisher Mosby.)

Systemic features

Lymphangiitis is unusual but there may be a mild tender regional lymphadenopathy. If untreated, three or four days after the development of the pustule there is a constitutional illness of high fever, toxaemia, prostration and subsequently delirium, collapse and death in a percentage of patients. In others the lesion heals within three weeks.

Management

A staphylococcal infection is the usual differential diagnosis but lymphangiitis is normally present. Cowpox, orf and cat-scratch disease are other possibilities. Pustules are rarely, if ever, present in anthrax lesions. The necrotic ulcer is usually painless which serves to differentiate from a spider bite. A biopsy may be useful for culture and histopathology. Ciprofloxacin 500 mg orally twice daily or alternatively doxycycline 100 mg orally twice daily are the antibiotics of choice.

Viral disorders of the skin 14

The common childhood ailments measles, rubella and erythema infectiosum, and the human herpesviruses, which cause herpes simplex (HHV-1 and HHV-2), varicella-zoster (HHV-3), Epstein–Barr virus infections (HHV-4), cytomegalovirus infections (HHV-5), roseola infantum (HHV-6) and Kaposi-associated herpesvirus (HHV-8), are described in this chapter. Also included are pox viruses, which cause vaccinia, smallpox, molluscum contagiosum and orf, human papilloma virus (HPV), which causes warts, Coxsackievirus (responsible for herpangina and hand, foot and mouth disease), and human immunodeficiency virus (HIV), the cause of the acquired immunodeficiency syndrome (AIDS).

Viraemia may result in an exanthem. The virus particles lodge in the dermal papillary loop. They may replicate and cause direct damage or an Arthus reaction, resulting in infarcts and haemorrhage. The latter occurs with the Rickettsiae. Most viruses, however, act as an inert foreign particle and cause a reaction by either reacting with circulating antibodies and sensitized lymphocytes or by forming immune complexes to produce a maculopapular rash.

DNA viruses may replicate in epidermal cells and cause vesicular lesions (pox viruses, herpes simplex and varicella-zoster). HPV and molluscа induce cell proliferation and induce tumours. RNA viruses do not usually enter epidermal cells and replicate but can produce a reaction before being removed (for example echoviruses, most toga viruses and rubella). The vesicular eruption of hand, foot and mouth disease is an exception. The picornaviruses include the enteroviruses, rhinoviruses (common cold virus) and hepatitis A. The enteroviruses were originally divided into three groups: polioviruses, which have no associated exanthem, Coxsackieviruses (type A producing herpangina and hand, foot and mouth disease; type B producing an epidemic pleurodynia, myalgia, myocarditis and pericarditis known as Bornholm's disease), and echoviruses, which may cause encephalitis, aseptic meningitis and diarrhoea and vomiting. Echoviruses do produce an exanthematic febrile illness with a rubelliform or morbilliform eruption that is difficult to distinguish from rubella clinically but may be distinguished serologically or by isolation of the virus in tissue culture and throat swab secretions, faeces and cerebrospinal fluid.

Measles (Rubeola)

A highly contagious viral infection of the upper respiratory tract and skin that may be followed by potentially serious secondary bacterial and neurological complications.

Aetiology

Measles is caused by an RNA virus of the paramyxovirus group. Its incidence dropped dramatically after the introduction of vaccination programmes but has risen once more following adverse publicity. It is most common in the spring and tends to occur in densely populated and socioeconomically depressed areas. It is spread via respiratory droplets. The rash results from a cell-mediated response. Leukaemic patients taking cytotoxic drugs that impair cell-mediated immunity do not get the rash with measles but do get a giant cell pneumonia or fatal encephalopathy. In normal individuals, a transient impairment of cell-mediated immunity exists for about a month after the rash, which may explain the susceptibility of these patients to tuberculosis and possibly to the invasion of the brain by measles virus, leading to subacute sclerosing panencephalitis many years later.

Clinical Features

Symptoms

The incubation period is 10–12 days. There follows a prodrome of fever, malaise, coryza and conjunctivitis, which resolve within a few days, and a cough, which may persist.

Morphology

The exanthem begins on the fourth day as conspicuous red macules and papules on the face (Fig. 14.1), behind the ears and on the upper part of the neck. It spreads cephalocaudally to the trunk and limbs within 3 days. The initial lesions coalesce (Fig. 14.2). Clearing occurs from the third day down the body, leaving behind a brown stain.

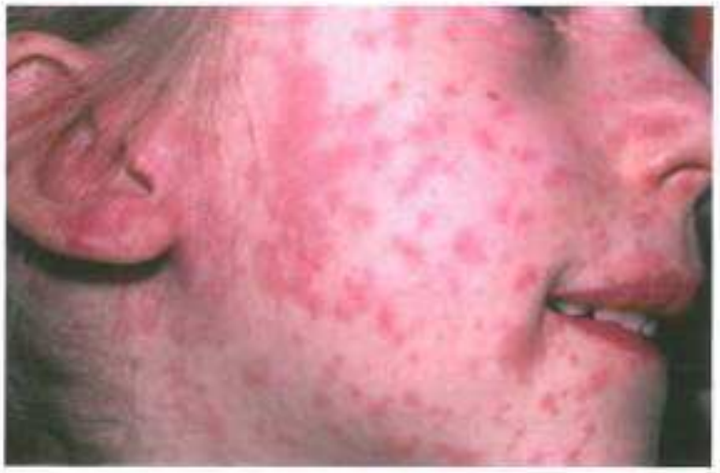


Fig. 14.1 Measles. Red macules and papules start on the face (in particular around the ears, cheeks and upper neck) on the fourth day.

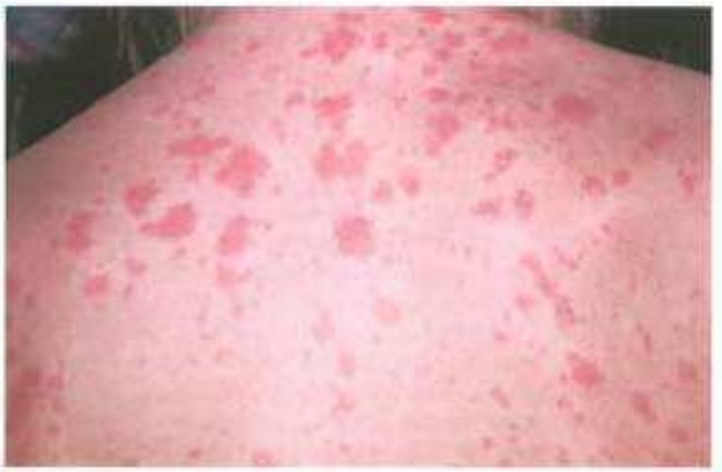


Fig. 14.2 Measles. The initial lesions coalesce and become blotchy (morbilliform). The patient is ill with fever, malaise, coryza and cough.

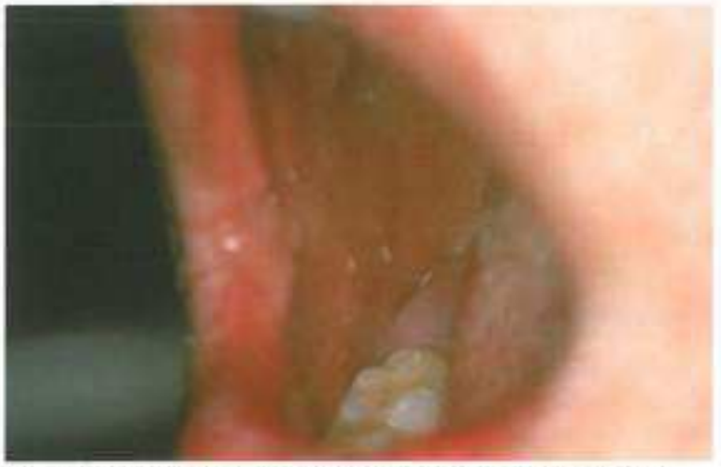


Fig. 14.3 Koplik's spots. Minute blue-white dots are present on the buccal mucosa during the prodrome. They disappear by the peak of the exanthem.

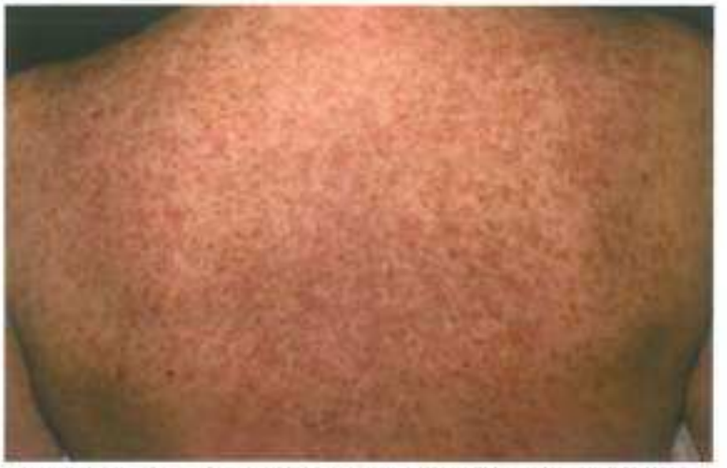


Fig. 14.4 Atypical measles. Epidemics of measles are recurring in the West and the disease is seen in adults who were either not vaccinated in infancy or had killed vaccine (withdrawn in 1976). (Courtesy of Dr Daniel Creamer.)

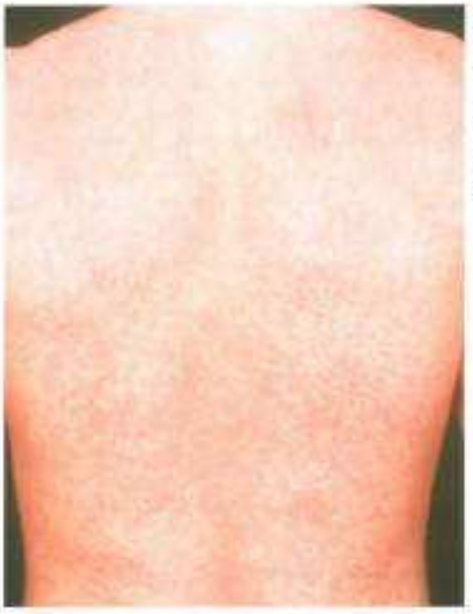


Fig. 14.5 Rubella. The exanthem spreads downwards from the face over 3 days. There is lymphadenopathy. It causes the congenital rubella syndrome and an arthritis in adults.

An enanthem, known as Koplik's spots, appears on the buccal mucosae during the prodrome. These are punctate, bluish white spots (Fig. 14.3) on a reddened base, which disappear by the peak of the exanthem.

Measles resolves within 14 days of the height of the eruption. It may be complicated by secondary bacterial infection (bronchopneumonia and otitis media) and occasionally by *postinfectious encephalomyelitis*, a serious demyelinating disorder with a significant mortality. A rare delayed complication is *subacute sclerosing panencephalitis*. It may occur months or years later and is progressive and fatal.

Atypical measles is less easy to recognize. It occurs almost exclusively in recipients of the killed vaccine who are subsequently exposed to measles. It primarily affects adolescents and young adults (Fig. 14.4) and has a significant morbidity. It commences with a high fever, headache, myalgia, nausea and vomiting and is followed in 2–4 days by a cough, pleuritic pain, photophobia and rash. Koplik's spots do not occur. The rash is rather variable but may be categorized into three varieties. The first consists of red macules and papules, which start around the distal extremities (palms, soles, wrists and ankles) and spread to the trunk and face. A second form consists of vesicles on a red base largely over the trunk, which resembles chickenpox, and a third form comprises petechiae over the trunk and extremities.

Management

The diagnosis is made by a fourfold rise in antibody titre between the acute and convalescent samples. Antibodies can also be measured in saliva. Leucopenia is usually present in cases uncomplicated by bacterial sepsis. A fine reticulonodular infiltrate of the lower lobes occurs in measles complicated by pneumonia and in all patients with atypical measles.

Clearly, prevention is better than cure. Live attenuated vaccine is available in a monovalent form for measles only, or in combination with vaccines for mumps and rubella (MMR), and is given at 15 months. Those with a dubious vaccination history or those who have previously received killed virus vaccine (which was withdrawn in 1976) should be revaccinated. Of these, 50% will have a reaction of mild erythema and swelling and slight constitutional symptoms. The vaccine is contraindicated in pregnancy.

Treatment of the disease is symptomatic except for complicated cases where antibiotics may be required.

Rubella (German measles)

A common viral infection affecting the skin, lymph nodes and joints. It is a benign condition except in the fetus.

Aetiology

It is caused by a single-stranded RNA togavirus infection, spreads by pharyngeal droplets, is very infectious in schoolchildren but may be asymptomatic. Adolescents and adults, however, usually develop symptoms. Epidemics occur in the spring.

Clinical Features

Symptoms

The incubation period is 14–21 days. A prodrome (not usually present in childhood) occurs briefly in older groups, lasts 1–5 days and consists of fever, headache, malaise, sore throat (but no coryza) and a suffusion and gritty sensation of the conjunctivae, which subside as the rash develops.

Morphology and distribution

The exanthem begins on the face and scalp and spreads downwards over the next 3 days. The lesions are very small, pink macules (Fig. 14.5), which may become papular and then confluent (Fig. 14.6) to form a diffuse erythema on the face, which clears after 24 hours, and then on the trunk, which clears on the third day; the limbs may continue with discrete lesions before clearing on the fourth day. Desquamation may occur. An enanthem of red petechiae may sometimes be observed on the soft palate (Fig. 14.7).

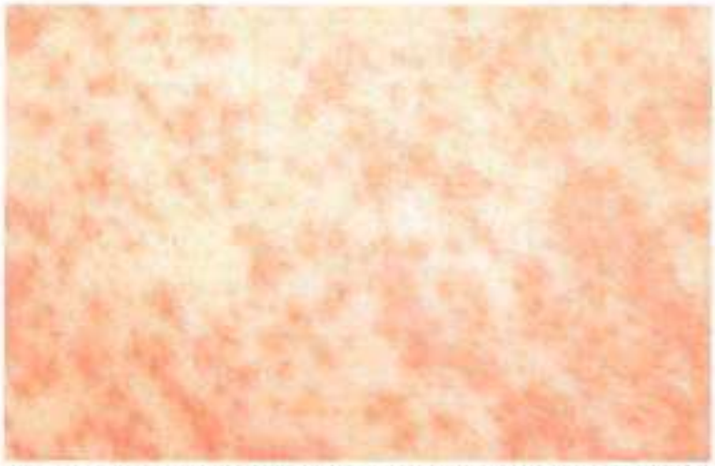


Fig. 14.6 Rubella. There are pink macules that become papular and desquamate.

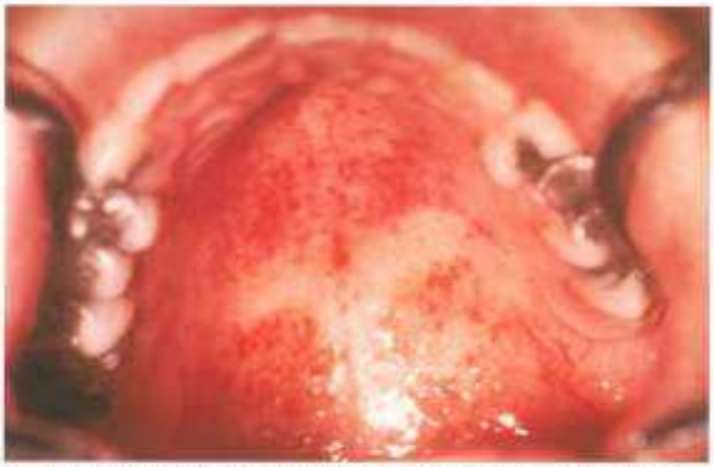


Fig. 14.7 Rubella. Petechiae may occur on the soft palate (Forscheimer spots).

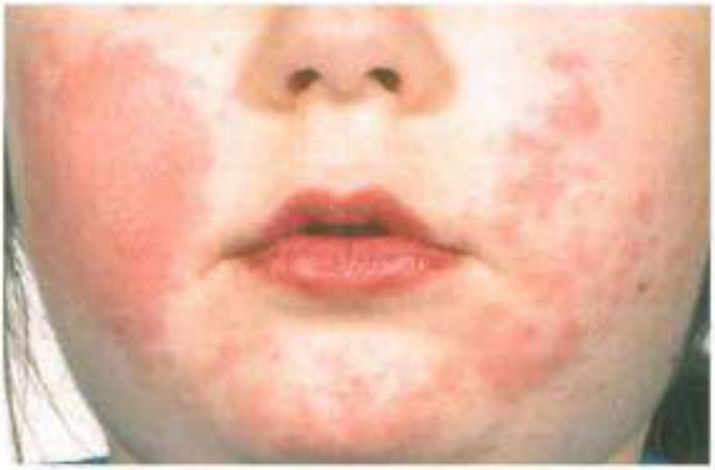


Fig. 14.8 Erythema infectiosum. There is a blotchy erythema that looks as if the cheeks have been slapped. It is caused by a parvovirus.

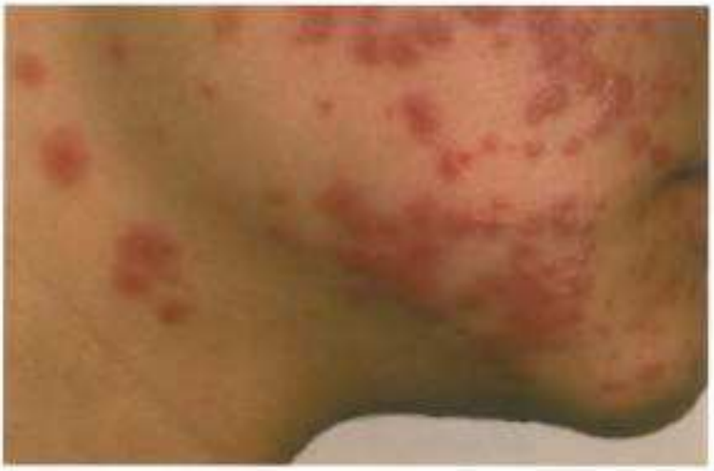


Fig. 14.9 Slapped cheek disease. This adolescent had pyrexia, malaise and headache followed by a facial eruption. She wanted to visit her pregnant sister but this was forbidden, which was fortunate because her serology was positive.

Systemic signs

There is a tender general lymphadenopathy that affects especially the postauricular, posterior cervical and posterior and suboccipital nodes; this may persist for some while. An arthritis particularly involving the fingers and wrists is common, especially in post-pubertal females. Effusions may be present. It persists for two weeks. Hepatitis, myocarditis, pericarditis, haemolytic anaemia, thrombocytopenic purpura and very occasionally encephalitis may occur.

Management

Rubella would be of no consequence but for the threat to the unborn child. All trimesters are at risk, although the greatest damage occurs in the first. Deafness, heart disease (especially patent duct) and cataracts are the most common complications of the *congenital rubella syndrome*. Stillbirth, abortions, prematurity and growth retardation are frequent. Encephalopathy, mental deficiency, diabetes mellitus and thyroid disorders are late sequelae.

A fourfold increase in antibody titres between specimens taken during and after the rash is diagnostic. A rubella-specific IgM title is raised for up to a month after the rash has gone. There is no treatment, so rubella vaccine should be given at 15 months as part of the MMR.

Erythema infectiosum (Fifth disease)

A parvoviral illness that is mild in children but is hazardous to the fetus; it may cause arthritis and occasionally pancytopenia in adults.

Aetiology

It is caused by human parvovirus B19, a small single-stranded DNA virus. It is more common in the winter and spring in youngsters. It is also known as fifth disease (fifth in classification after measles, scarlet fever, rubella and a fourth illness that is no longer considered a distinct entity).

Clinical Features

Symptoms

After an incubation period of about 10 days, there is a mild prodrome of slight pyrexia, malaise and headache. The rash begins a few days later.

Morphology and distribution

There is a striking red, raised erythema over the cheeks (hence 'slapped cheeks'; Figs 14.8 and 14.9); followed by a symmetrical reticular papular

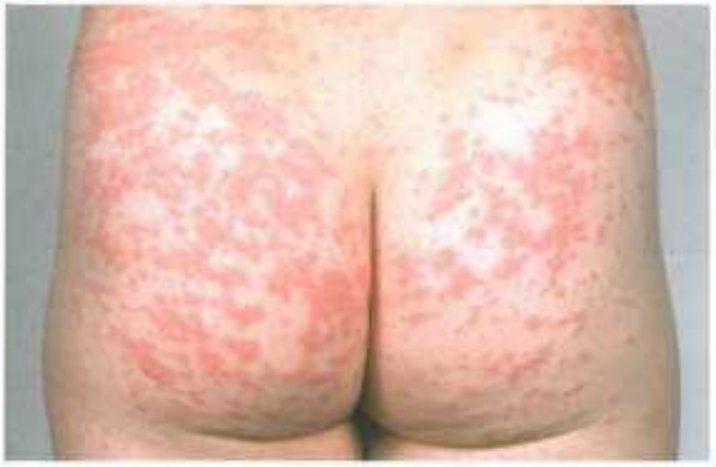


Fig. 14.10 Erythema infectiosum. The buttocks are affected with a symmetrical reticulate papular eruption. It is hazardous to the fetus.

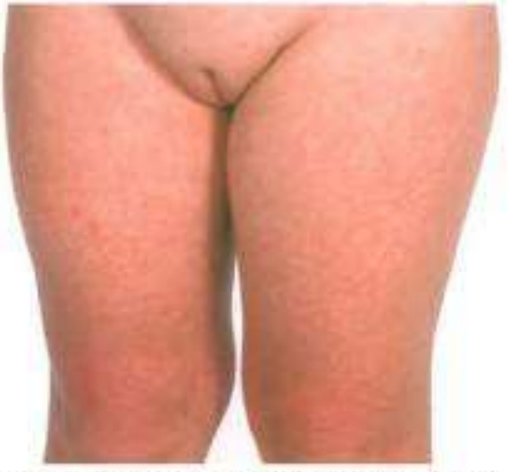


Fig. 14.12 Roseola infantum. There is a high fever for 4 days, which suddenly disappears when the red macules appear.

eruption on the buttocks (Fig. 14.10) and on the extensor surfaces of the limbs (Fig. 14.11). It lasts a week or two, with a tendency to flare before complete resolution.

Systemic signs

Erythema infectiosum has a greater morbidity in adults than in children in that a transient symmetrical arthritis may occur, which involves particularly the wrists, ankles and knees, particularly in women. It is occasionally persistent. Adults may have no eruption or a lace-like erythema of extensor surfaces and buttocks preceded by an influenza-like illness, fever, sore throat, myalgia and lymphadenopathy.

Management

Erythema infectiosum is a hazard to pregnant women and may cause fetal death. It may precipitate aplastic anaemia, particularly in patients with sickle cell anaemia.

Viral particles are identifiable by electron microscopy in serum, urine and respiratory secretions early in the disease. The diagnosis can also be made serologically. IgM antibodies to parvovirus are positive for a couple of months and IgG antibodies persist indefinitely.

Treatment is symptomatic. Pregnant women exposed to suspected or confirmed cases should be screened for antibodies and managed accordingly. There is no vaccine.

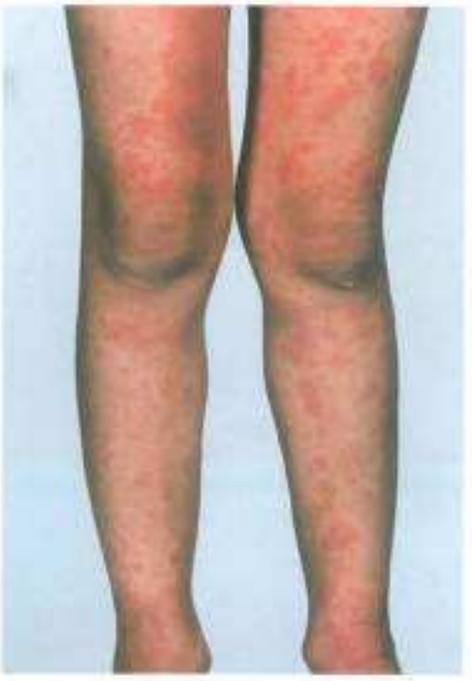


Fig. 14.11 Slapped cheek disease. The lesions may be more extensive and occur in the limbs as a reticulate and blotchy erythema as in this 6-year-old. The diagnosis is easily made serologically.

Roseola infantum (Exanthem subitum)

A common viral infection of infancy, characterized by an abrupt onset of high fever, which subsides after four days, when a rash appears.

Aetiology

It is caused by HHV-6 and HHV-7, which was first isolated in patients with AIDS and lymphoproliferative disorders. Approximately 90% of the population are infected with it by the age of 2 years. It also causes a febrile illness without a rash, an infectious mononucleosis-like illness, sinus histiocytosis and a *glove and sock syndrome* (a painful erythema and purpura in a glove and stocking distribution. Parvovirus and Coxsackie B6 produce a similar condition.). It is transmitted from mother to child via saliva and shows tropism for $CD4^+$ lymphocytes, causing large ballooning cells and syncytia, as well as for other cells. There is lifelong latency. The virus may be reactivated during immunosuppression, including during organ transplantation, and this may be responsible for the more severe forms of graft-versus-host disease. The reactivated virus may also be involved in a severe drug-induced hypersensitivity syndrome (DRESS, Ch. 18). It seems that this is a similar phenomenon to that noted between Epstein–Barr virus and ampicillin and to the greatly increased risk that patients with AIDS have of developing drug hypersensitivity.

Clinical Features

Symptoms

The incubation period is 7–14 days. There is no prodrome but the onset is abrupt with a high fever (39.5–40°C), sometimes associated with convulsions. The exanthem appears with defervescence. There may be cervical and occipital lymphadenopathy.

Morphology

Discrete rose pink macules and papules are short lived, lasting a few hours or at most a couple of days. An enanthem of red macules or streaks may be observed on the soft palate during the feverish stage.

Distribution

It begins on the neck, especially behind the ears, and spreads to the trunk and limbs (Fig. 14.12).

Management

The sudden (Latin: *subitum*) onset of the rash and cessation of the fever usually gives the diagnosis. There is a leucopenia during the fever, and antibodies for HHV-6 are detectable within 2 weeks. There is no vaccine or specific treatment of the febrile convulsions, which, fortunately, rarely have long-term sequelae.

Herpes simplex

An acute self-limiting but recurrent affliction of the skin and mucous membranes caused by a latent double-stranded DNA virus, HHV-1 and HHV-2.

Aetiology

It is a common contagious mucocutaneous infection. HHV-1 was originally only associated with oral and facial infections, but because of the increasing frequency of orogenital sex, is now responsible for a number of genital infections. HHV-2 is most common on the genitalia and buttocks.

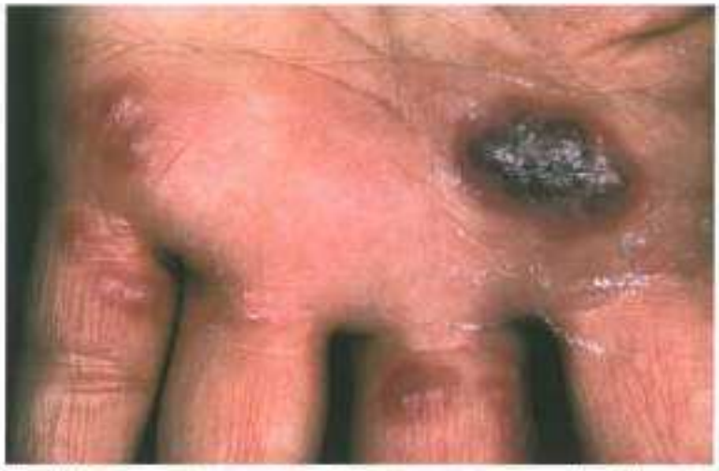


Fig. 14.13 Primary herpes simplex. There are extensive grouped vesicles surrounded by erythema. Type 2 herpes simplex was cultured from vesicle fluid.

It may be oncogenic, since carcinoma of the cervix is more common in females who have had genital herpes or who have HHV-2 antibodies.

The condition begins as a primary infection, which may be subclinical. In childhood, the infection is usually acquired by droplet infection or by direct contact, for example being kissed by an afflicted parent or friend. Rugby football players are at risk ('scrumpox') from contact with another player who has the active disease. Other contact-sportsmen (e.g. wrestlers) run the same risk (herpes gladiatorum). Patients with atopic eczema are particularly vulnerable to the virus. Typically primary infection with HHV-1 is either a gingivostomatitis or widespread eruption on the face. Primary HHV-2 infection usually occurs after sexual activity has commenced and presents as either a vulvovaginitis or balanitis. It can occasionally occur in childhood and may result from sexual abuse.

Following the primary attack, the virus is latent and resides in the sensory nerve ganglion. Recurrences occur in some individuals but not in others and vary in frequency, often decreasing with time. Ultraviolet light, mild upper respiratory tract infections, local trauma, menstruation and stress may precipitate attacks. Patients who have antibodies to herpes simplex and contract lobar pneumonia, meningococcaemia infections or malaria always develop lesions ('fever blisters') even if they have never had it before. Prior infection with HHV-1 does not protect against HHV-2.

All children living in crowded conditions in underdeveloped countries have antibodies to HHV-1 but only 50% of British undergraduates.

PRIMARY INFECTION

Clinical Features

Symptoms

The onset is sudden, with fever, extensive grouped painful small blisters and often with regional lymph node swelling.

Morphology

There are extensive grouped macules; these rapidly become painful vesicles (Fig. 14.13) that erode and form crusts (Fig. 14.14).

Distribution

In HHV-1 infections, the lips, face (Fig. 14.15) and inside of the mouth (gingivostomatitis) may be involved. The patient is uncomfortable and

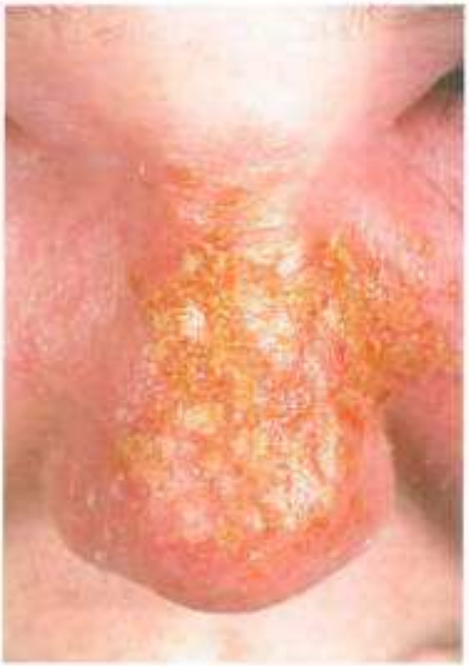


Fig. 14.14 Primary herpes simplex. There is erythema and oedema and pronounced yellow crusting of the vesicles, which can simulate impetigo.

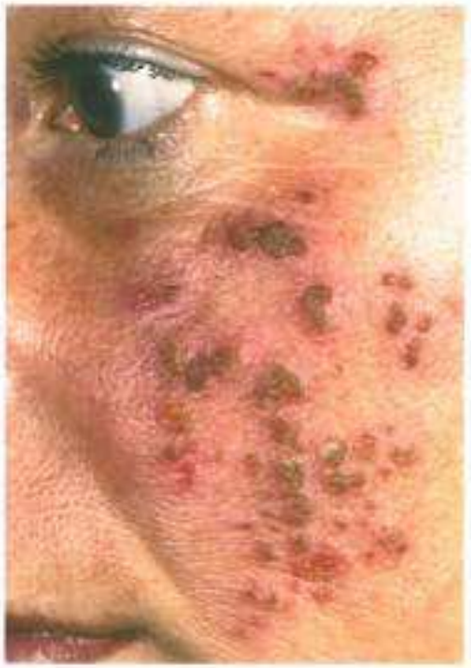


Fig. 14.15 Primary herpes simplex. Grouped scabbed lesions surrounded by erythema are present.

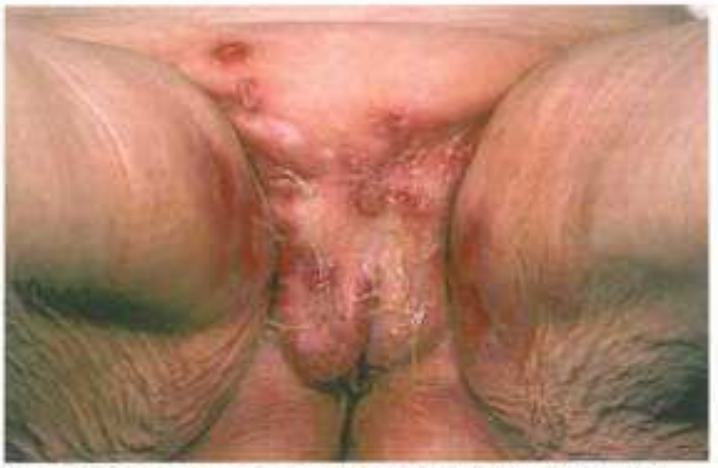


Fig. 14.16 Primary herpes simplex. The genitalia are frequently involved in human herpesvirus type 2 infections. Grouped vesicles are present.

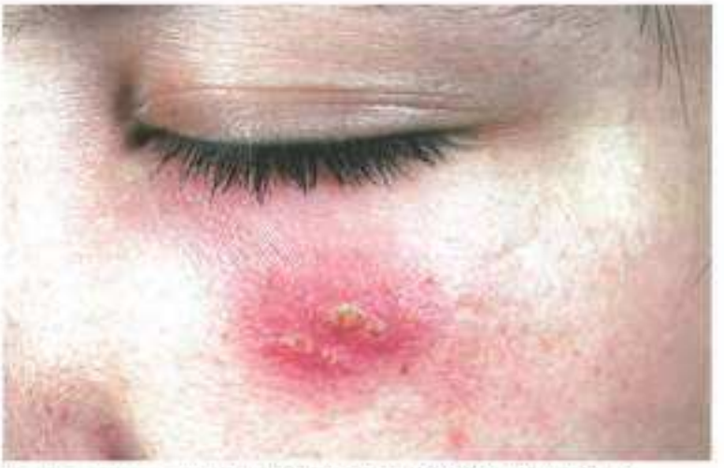


Fig. 14.17 Herpes simplex. There is a cluster of vesicles surrounded by erythema. They dry, scab and heal within two weeks without scarring, but leave temporary post-inflammatory pigmentation in some.

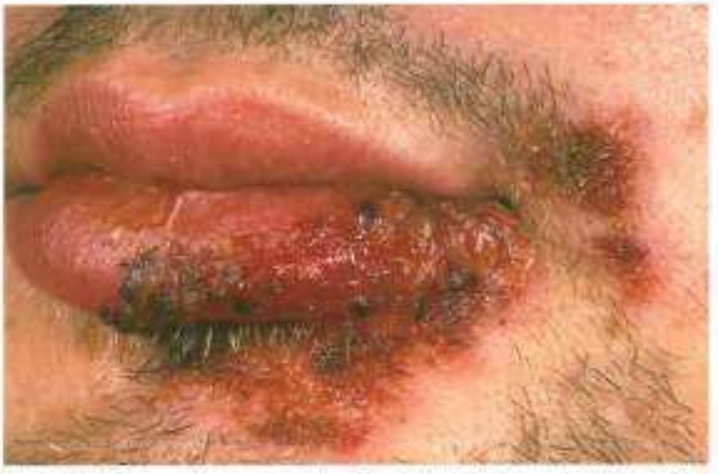


Fig. 14.18 Recurrent herpes simplex. The 'cold sore' occurs most commonly on the lips, and recurrences are often frequent. This eruption is more extensive than usual and he was found to be HIV positive.

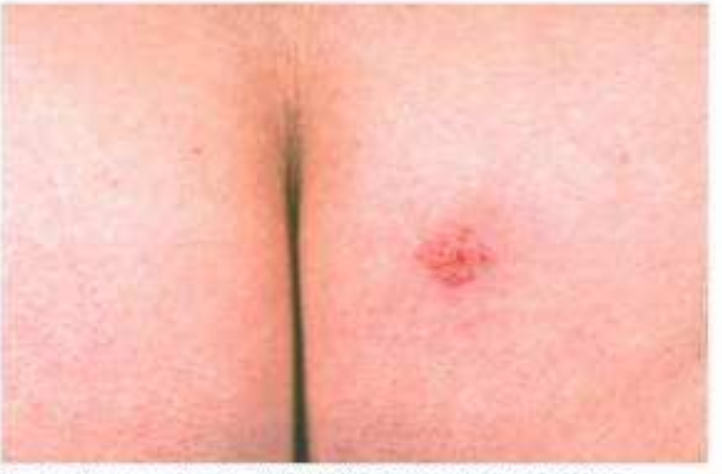


Fig. 14.19 Herpes simplex. Although the diagnosis is easy on the face, sometimes infections at other cutaneous sites, particularly the buttock, cause difficulties.

unwell and may find it impossible to eat satisfactorily. In HHV-2 infections, the genitalia (Fig. 14.16) are involved and urinary retention may result. Regional lymphadenopathy is present.

RECURRENT HERPES SIMPLEX

Clinical Features

Symptoms

It begins with a tingling or discomfort in the skin, followed by blisters.

Morphology

Vesicles (Fig. 14.17) surrounded by erythema evolve rapidly from macules and papules and are found in clusters. They coalesce, become dry and scab (Fig. 14.18) and usually heal without scarring, although postinflammatory hyperpigmentation may be present. The attack lasts 5–10 days.

Distribution

It can recur anywhere on the integument (Fig. 14.19). The genitals (Fig. 14.20) and buttocks have become common sites. The infection may be

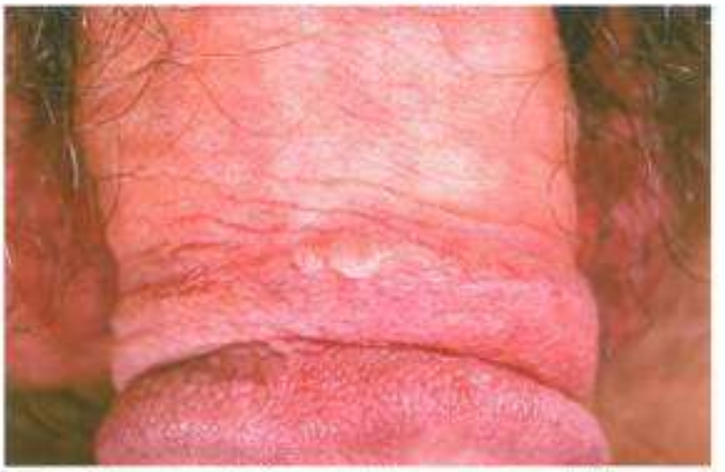


Fig. 14.20 Herpes simplex. Grouped vesicles occur on the genitalia from sexual contact.

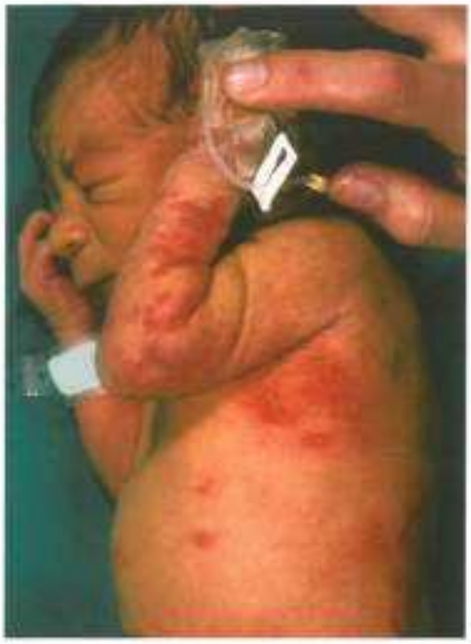


Fig. 14.21 Neonatal herpes simplex. Vesicles surrounded by erythema are present. Type 2 herpes simplex was cultured from the mother's birth canal.

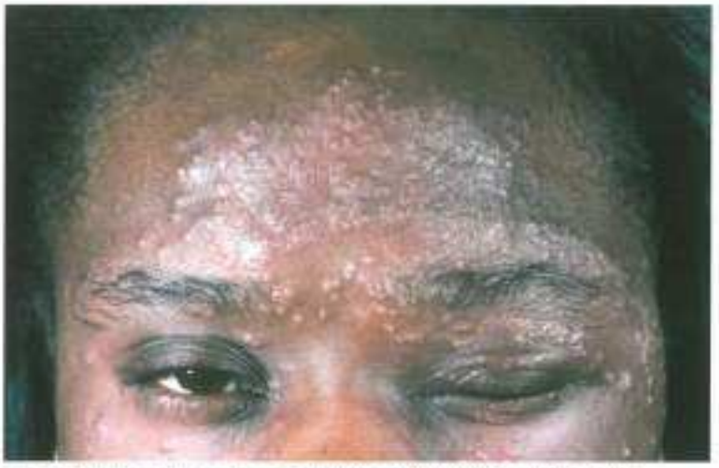


Fig. 14.22 Eczema herpeticum. There is a widespread vesicular eruption causing oedema. This patient had atopic eczema, which has become superimposed with herpes simplex.

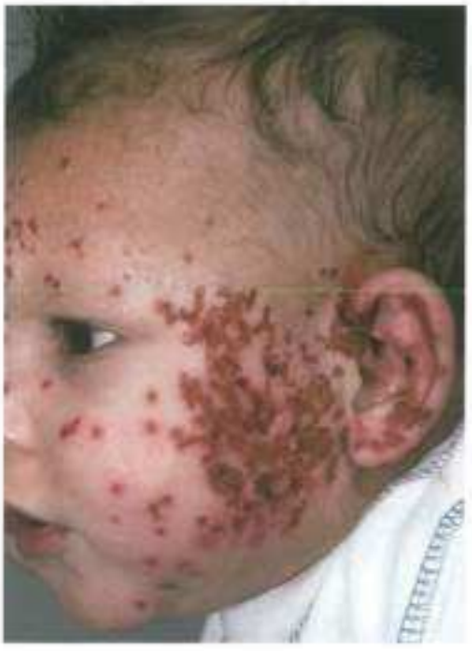


Fig. 14.23 Eczema herpeticum. This infant had minor atopic eczema, but these patients are vulnerable to certain viruses (herpes simplex, molluscа and vaccinia). He was misdiagnosed by his paediatrician as having impetigo: a common error, but the discrete vesiculopapules should suggest herpes simplex.

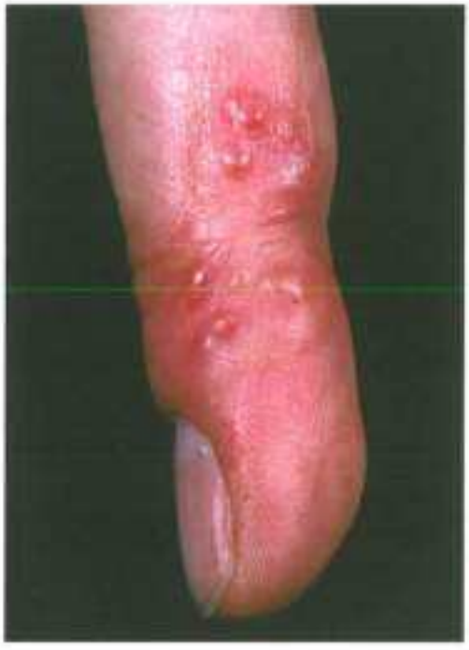


Fig. 14.24 Herpes simplex. Medical personnel and dentists may unwittingly contract the virus on a finger from tending an infected patient.

limited to the cervix and be asymptomatic; as a result the disease is unwittingly transmitted.

Complications

- **Maternal genital infection and delivery** The newborn has no natural immunity and is, therefore, at risk of systemic infection (Fig. 14.21) if maternal genital infection, often primary HHV-2, coincides with delivery. Caesarean section is advisable if smears from the birth canal are positive.
- **Disseminated herpes simplex infection** The immunosuppressed are at risk.
- **Kaposi's varicelliform eruption (eczema herpeticum)** Atopics are at risk of widespread herpes simplex infections (Figs 14.22 and 14.23).
- **Herpetic whitlow** This is a primary infection on a finger (Fig. 14.24), often inoculated from an infected patient. Medical and dental personnel are particularly at risk (Fig. 14.25).

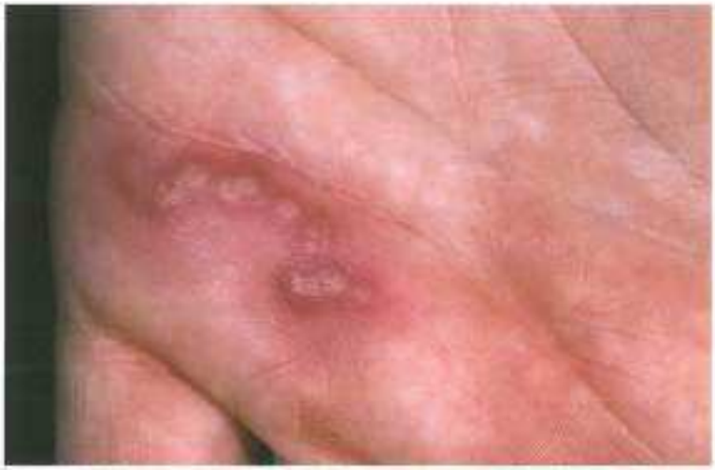


Fig. 14.25 Herpes simplex. This patient was an anaesthetist and unwittingly contracted the infection whilst anaesthetising a patient who had herpes simplex.

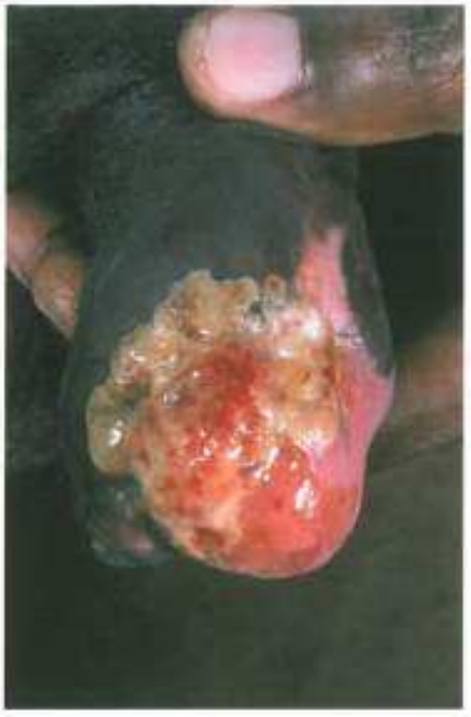


Fig. 14.26 Chronic genital herpes simplex. In immunosuppressed individual patients (he was HIV positive), persistent ulceration may occur. PCR was positive for herpes simplex. He responded to ganciclovir.

Fig. 14.27 Erythema multiforme. A minority develop erythema multiforme with target lesions (illustrated here) each time they develop herpes simplex.

- **Keratoconjunctivitis** Herpes simplex causes a purulent conjunctivitis. Corneal ulceration and blindness may result. The surrounding skin may be involved and the preauricular glands enlarged.
- **Chronic perianal and genital herpes simplex in immunosuppressed patients** (Fig. 14.26). Persistent ulceration of the skin following a vesicular eruption may occur in HIV-positive individuals, and in chronic lymphatic leukaemia.
- **Erythema multiforme** A minority suffer from recurrent erythema multiforme (Fig. 14.27) precipitated by herpes simplex. Viral DNA may be identified by the polymerase chain reaction in skin lesions.
- **Radiculoneuropathy** Particularly following perianal disease, there is sacral paraesthesia, urinary retention, constipation and impotence. Recovery occurs after a few weeks.
- **Aseptic meningitis** Approximately 8% may develop this following primary genital herpes simplex.
- **Zonal herpes simplex** It is occasionally difficult to distinguish herpes zoster clinically from herpes simplex in a zonal distribution (Fig. 14.28). Virology is required for precise distinction.
- **Herpesphobia** On the face, it is temporarily and tiresomely disfiguring but on the genitalia it can give rise to considerable distress and anxiety.

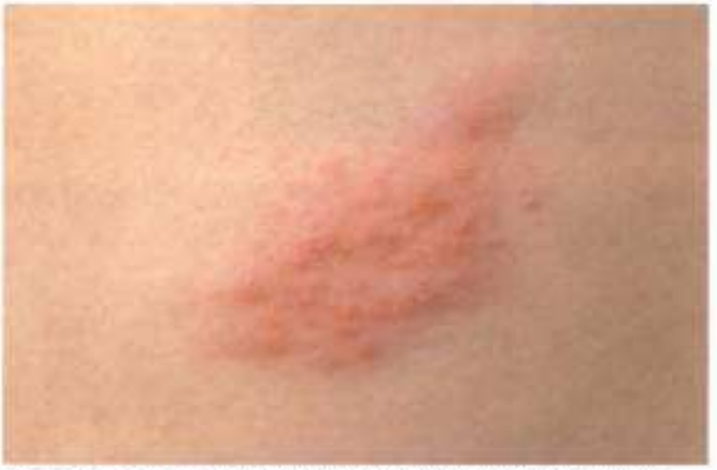


Fig. 14.28 Zonal herpes simplex. There are grouped vesicles in a linear but limited distribution. Culture was positive for herpes simplex.

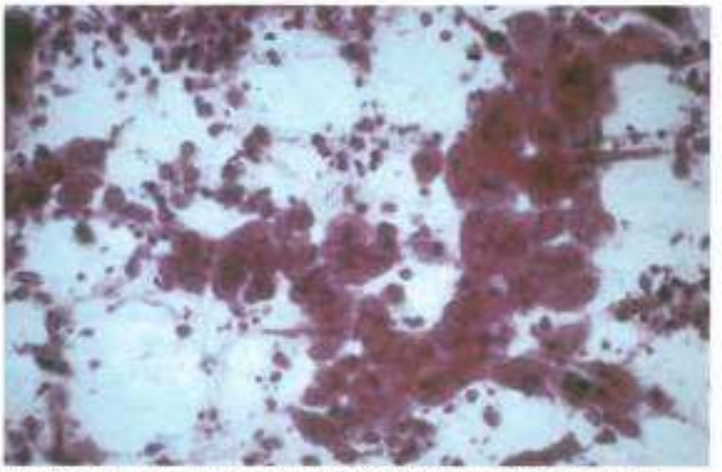


Fig. 14.29 Herpes simplex. Tzanck test. Cytodiagnostic techniques reveal multinucleated giant cells with degenerate nuclei ('balloon degeneration') in herpes simplex.

Management

The diagnosis of recurrent herpes simplex can usually be made from the history if the patient does not have an active eruption. It can be confirmed by taking a swab for culture or polymerase chain reaction (PCR). The virus may also be visualized in the vesicle fluid under the electron microscope. Cytodiagnosis shows characteristic bizarre multinucleate giant cells with degenerate nuclei ('balloon degeneration'), which result from infection of epithelial cells (Fig. 14.29). Similar changes are seen with varicella-zoster infections. Histologically, the infected epithelial cells are swollen. Intranuclear inclusions occur and, typically, giant cells form (Fig. 14.30) containing several nuclei. Vesicles result from intra- and intercellular oedema. Polymorphonuclear leucocytes invade both the dermis and epidermis.

Aciclovir

Aciclovir is an acyclic analogue of deoxyguanosine and a specific inhibitor of thymidine kinase, which is only present in herpesvirus-infected cells. Aciclovir has low clinical toxicity (headaches, nausea, vomiting or diarrhoea). It is not mutagenic, carcinogenic or teratogenic at therapeutic doses.

- **Topical aciclovir** Aciclovir 5% cream should be applied immediately the premonitory symptoms are felt and then five times daily for 5 days to abort attacks. It does not prevent further attacks.
- **Systemic therapy** Oral aciclovir, 200 mg five times a day for 5 days, or intravenous aciclovir, is indicated for:
  - — severe primary infections
  - — eczema herpeticum
  - — disseminated herpes simplex
  - — herpes simplex in immunosuppressed patients
  - — frequent recurrences.
- **Prophylactic systemic therapy** Continuous oral aciclovir (200 mg three times daily or 400 mg twice daily) reduces recurrences sevenfold in patients who have frequent outbreaks. Side-effects other than mild gastrointestinal symptoms in a few patients are unusual, but the disorder may recur on stopping the treatment, often in a rebound manner.

Other systemic agents

Valaciclovir is an L-valine ester prodrug of aciclovir. It is rapidly and almost completely converted to aciclovir after oral administration but its bioavailability is three to five times that of aciclovir and it is as effective as aciclovir, in a dose of 1 g twice daily for treatment of herpes simplex. Famciclovir has a half-life that is ten times greater than aciclovir (so less frequent doses are needed), and is effective in some forms of resistant aciclovir strains but is more toxic (especially renal) and has to be delivered intravenously. Cidofovir is also effective against resistant strains. Zidovudine is active against type 1 herpes simplex but not type 2.

Chickenpox (Varicella)

A common disorder of youth caused by the varicella-zoster virus.

Aetiology

Chickenpox and herpes zoster are both caused by HHV-3. The virus is aerolized from vesicular fluid from an infected contact. It enters the respiratory tract and replicates in nasopharyngeal lymphoid tissue from where T cells home to the skin causing chickenpox and then to the dorsal root or cranial nerve ganglion where it lies dormant but may subsequently reactivate as herpes zoster. It occurs worldwide and in epidemics. An attack confers lasting immunity. Maternal or administered antibodies do not prevent chickenpox but do reduce the severity of the infection in infants. Patients with impaired cell-mediated immunity may have severe chickenpox and are at risk of herpes zoster, but those with agammaglobulinaemia are not at risk.

Clinical Features

Symptoms

Following an incubation of 9–23 days, there is a mild prodrome of fever and malaise for 2 days, with a fleeting erythema. Chickenpox is pruritic.

Morphology

Crops of macules, which become vesicles surrounded by erythema, appear. Their contents become turbid and crusted and, in the absence of secondary infection, heal without scarring. Individual lesions are at different stages of development (Fig. 14.31).

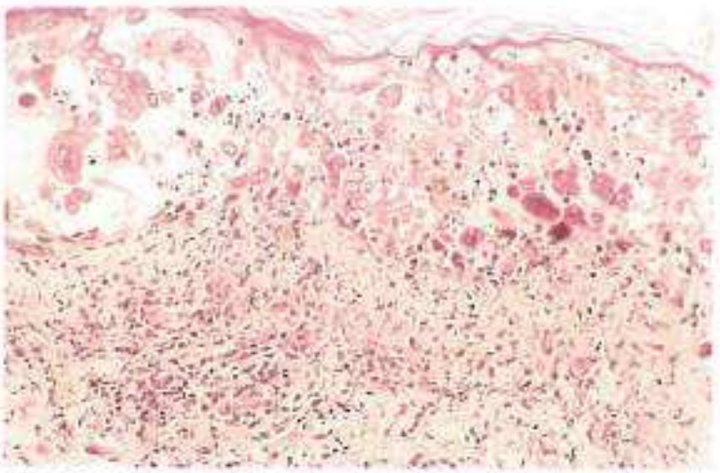


Fig. 14.30 Herpes simplex. Histology shows intra- and intercellular oedema with swollen infected epithelial cells, intranuclear inclusions and giant cells.

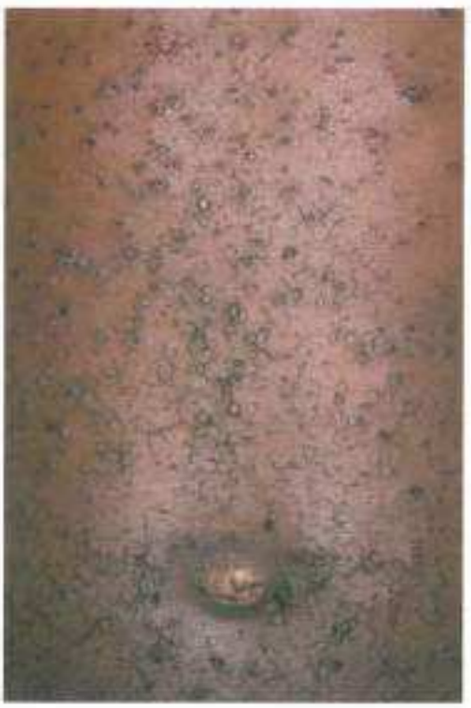


Fig. 14.31 Chickenpox. The face and trunk are particularly involved. The lesions are at different stages of development but the helpful diagnostic lesion is the vesicle surrounded by erythema.

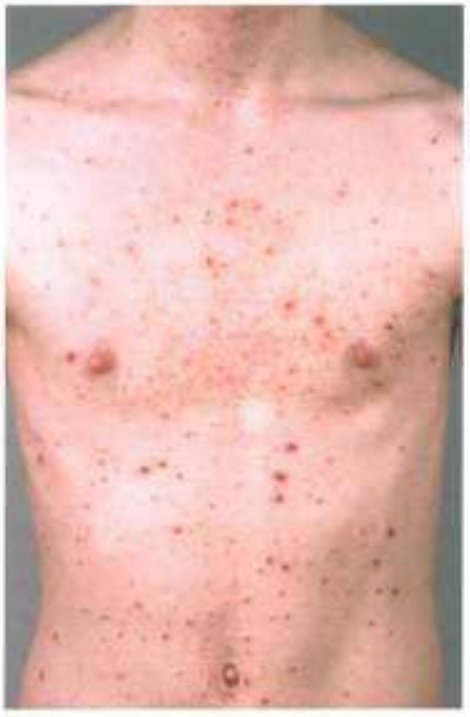


Fig. 14.32 Chickenpox. The distribution is centripetal, the trunk being predominantly affected. The lesions are at various stages of evolution.

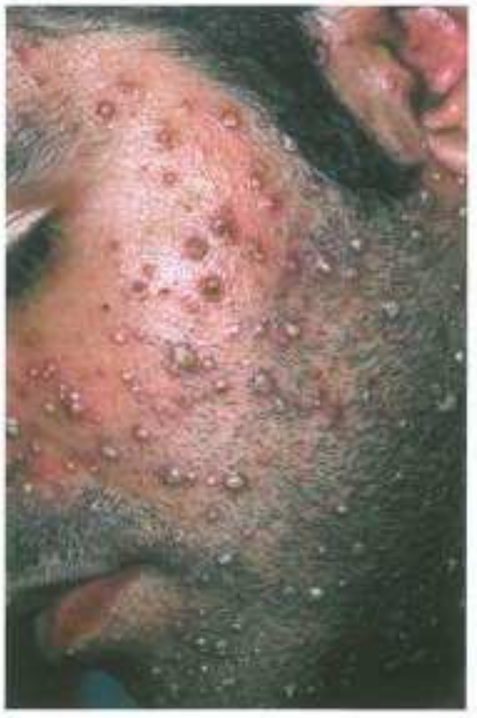


Fig. 14.33 Secondarily infected chickenpox. The vesicles of varicella are clear or turbid but in secondary bacterial infection (usually caused by *S. aureus*) they are yellow and pustular. Antibiotics are required in addition to antiviral therapy.

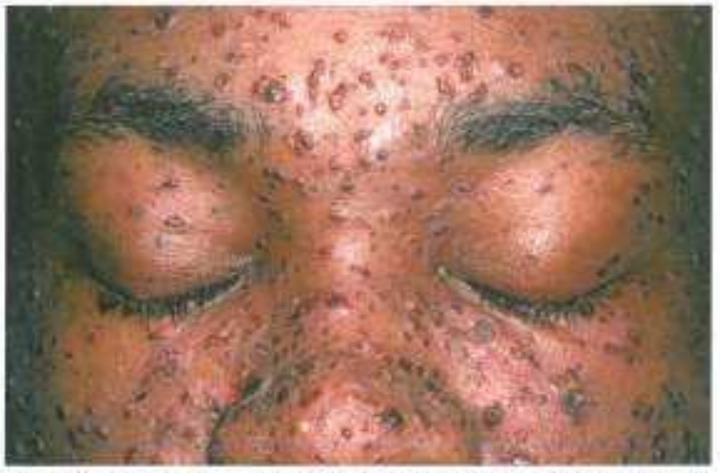


Fig. 14.34 Chickenpox. The face is affected with vesicles that become scabbed and usually result in one or two scars.

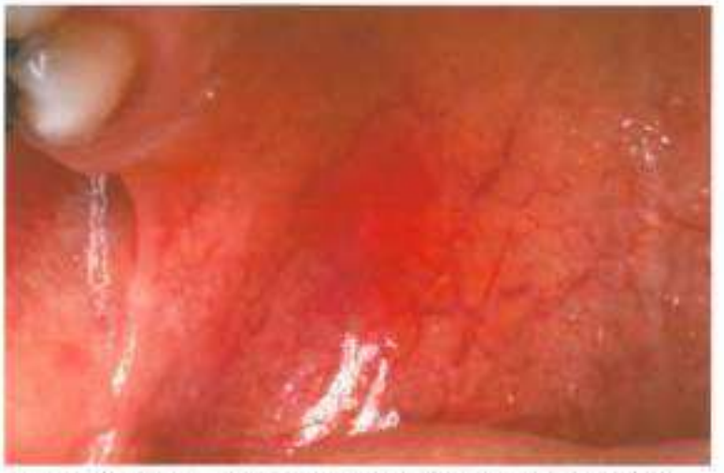


Fig. 14.35 Chickenpox. Vesicles surrounded by erythema are normally to be found in the mouth.

Distribution

The trunk is most extensively affected (Fig. 14.32), then the face (Figs 14.33 and 14.34) and scalp, followed by the upper arms and thighs. The forearms and lower legs are less affected (a centripetal distribution). Lesions are found in the mouth (Fig. 14.35).

Subclinical infections may occur. Vesicle fluid contains the virus but not the scabs; when the latter appear the patient is no longer infectious.

Complications

Complications are unusual except in neonates and the immunosuppressed.

- **Neonates** Maternal chickenpox in the perinatal period is life threatening because the neonate has no immunity to chickenpox and may develop severe disease with a significant mortality without treatment. Maternal infection in the earliest weeks of pregnancy can occasionally cause fetal eye defects.
- **Haemorrhagic varicella** In the immunosuppressed, for example those with lymphoma, leukaemia, tuberculosis and AIDS and those taking immunosuppressants, there may be haemorrhage into the vesicles and high fever and severe constitutional upset.
- **Secondary infection** Infection of two or three lesions is usual but extensive infection with septicaemia is rare, except in the tropics.
- **Other complications** Thrombocytopenic purpura and encephalitis are rare but recovery is usual. Varicella pneumonia occurs in neonates and the immunosuppressed: widespread miliary mottling is evident on radiographs.

Management

HHV-3 is easily demonstrated by electron microscopy of vesicle fluid and found with PCR. It can also be grown in tissue culture, and complement-fixing antibodies in convalescent sera can be titrated against acute specimens. The indications for treating varicella with systemic agents are the

immunosuppressed, children with eczema and adults with varicella. The disadvantage of treating normal children is that it may impair their long-term immunity to the virus.

- **Aciclovir** Systemic aciclovir, 800 mg five times daily orally or 500 mg three times daily for 5 days intravenously, is effective at reducing the number of lesions and causes defervescence but does not reduce the complications of varicella pneumonia, encephalitis, cerebellar ataxia or bacterial superinfection.
- **Other drugs** Valaciclovir and famciclovir.
- **Antibiotics** Appropriate antibiotics should be given for widespread cutaneous or other bacterial complications.
- **Varicella-zoster immunoglobulin** This should be given to neonates exposed to chickenpox.
- **Vaccine** Live attenuated vaccine hijacks the skin homing cells and reduces the incidence of infection by half.

Herpes zoster

A painful affliction of cutaneous nerves resulting from a reactivation of a dormant varicella-zoster virus (VZV), commonly known as shingles.

Aetiology

Herpes zoster (Greek *zoster*: belt) is a common infection caused by HHV-3, an enveloped double-stranded DNA virus and the same virus that transmits chickenpox (VZV). The virus lies dormant in the dorsal root or cranial nerve ganglion after a patient recovers from chickenpox, and antibodies are present in the serum. There may be a latent period of several decades before the virus is reactivated and commences to spread along the cutaneous nerve. Antibody titres are high in the acute stage of zoster and even higher during convalescence, which indicates that an amnestic response occurs.

There is no convincing evidence that shingles can be contracted from another individual. The reactivation of the virus is probably precipitated by waning immunological surveillance of the dormant virus. Patients with leukaemia, lymphoma, multiple myeloma, taking systemic steroids or undergoing immunosuppression during organ transplantation (especially marrow) frequently develop the disease, often in a disseminated form. Absolute leucopenia correlates with severe systemic involvement. Infections such as tuberculosis, syphilis, malaria and AIDS predispose to zoster.

Live chickenpox virus is present in the lesions of shingles until the scabs have formed. Therefore, an individual who has never had chickenpox can contract it from a patient with shingles, although zoster is less contagious than varicella, because oropharyngeal lesions are less common.

The disease is more common in the elderly. Overall the thoracic nerves are the most commonly affected, followed by the trigeminal (particularly in the elderly), cervical, lumbar and sacral. Second attacks of zoster are rare (4%).

Clinical Features

Symptoms

There is an abrupt onset of pain or discomfort. It is peculiarly distracting.

Morphology

Each lesion begins as a red macule, which rapidly becomes a papule and then a vesicle surrounded by erythema. These become confluent (Fig. 14.36). Over the next 2–3 weeks, the lesions become pustular, haemorrhagic and finally scab. As the scabs fall off, white scars may result. At any one time, the actual lesions are at various stages of development and there are usually a few satellite lesions, which may be widespread in the immunosuppressed, found away from the affected dermatome. The vesicle is very characteristic of the eruption. Secondary bacterial sepsis with either *Staphylococcus aureus* or *Streptococcus pyogenes* is common and there is usually regional lymphadenopathy.

Distribution

Examination reveals an eruption that is limited to one side of the body and corresponds to a dermatome (Figs 14.37 and 14.38).

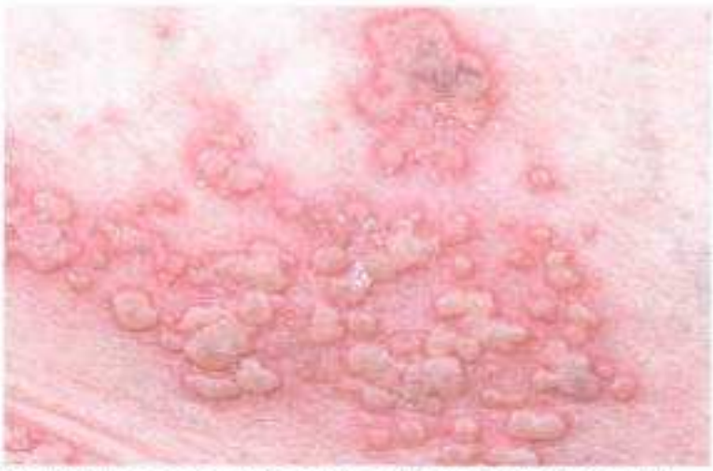


Fig. 14.36 Herpes zoster. Pain is accompanied by red macules that rapidly become vesicles surrounded by erythema.

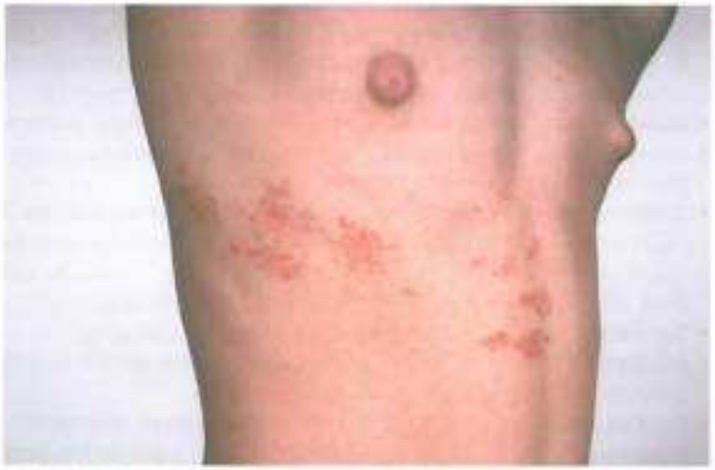


Fig. 14.37 Herpes zoster. The commonest site affected is the torso. It occurs unilaterally like a belt (Gk: zoster) in a dermatomal distribution (here: T8).

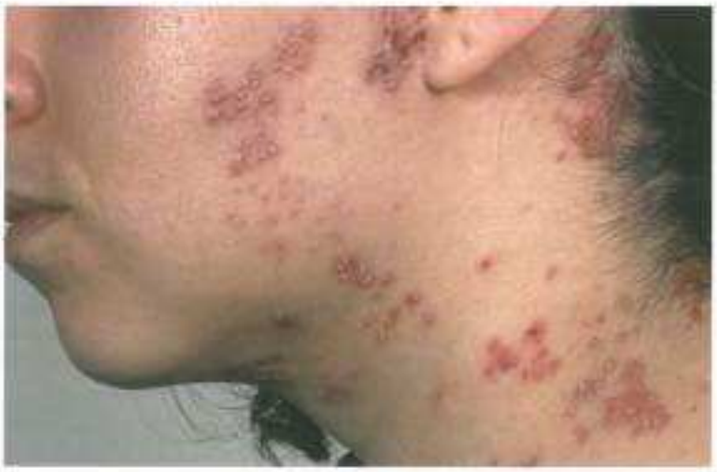


Fig. 14.38 Herpes zoster. There are vesicles surrounded by erythema. The dermatomal distribution gives away the diagnosis.

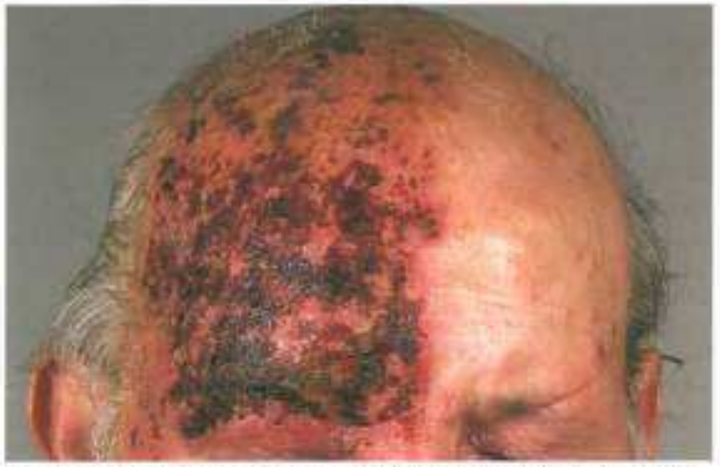


Fig. 14.39 Herpes zoster. The trigeminal is the most frequently involved cranial nerve and is the nerve most often affected in the elderly. The eye may be affected if the ciliary ganglion is involved, in which case the side and tip of the nose will be affected.

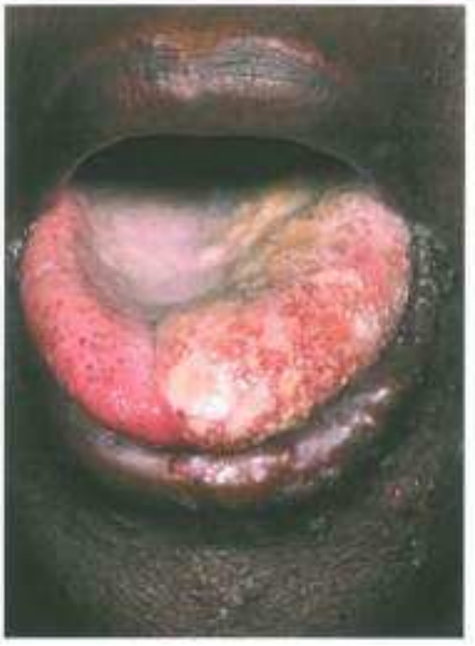


Fig. 14.40 Herpes zoster. The anterior two-thirds of the tongue is affected when the mandibular branch of the trigeminal nerve is involved.

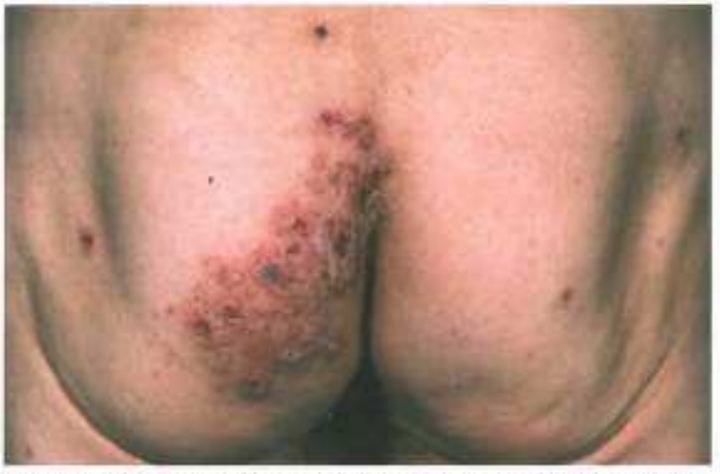


Fig. 14.41 Herpes zoster. Herpes zoster affecting the sacral nerve may lead to urinary and faecal retention.

Complications

For most individuals an attack of shingles is a tiresome interlude of 2–3 weeks during which they feel unwell and uncomfortable, although they make a full recovery with no sequelae. However, there are various complications from the involvement of certain dermatomes.

- **The ophthalmic branch of the trigeminal nerve** (Fig. 14.39) If the nasociliary ganglion is involved, the eye may be affected causing keratitis and iritis potentially leading to blindness, in which case the side and tip of the nose will be involved (Hutchinson's sign).
- **Ramsay Hunt's syndrome** If the geniculate ganglion is involved, facial palsy may result. The ear is painful and vesicles are present on the pinna and in the external auditory canal. The facial nerve is essentially a motor nerve but it has vestigial sensory fibres supplying the pinna, meatus, tonsillar fossa and soft palate. Swelling of these infected sensory nerves compresses the motor fibres in the confines of the facial canal and the internal auditory meatus causing the facial palsy.
- **The mandibular branch of the trigeminal nerve** The anterior two-thirds of the tongue (Fig. 14.40) chin and side of face are affected.
- **Sacral nerve involvement** Involvement of the anogenital region (Fig. 14.41) may lead to retention of urine and difficulties with defaecation.
- **Postherpetic paralysis** Motor involvement occurs in 5%. Paralysis (usually temporary) results from disruption of motor nerves involved by the dermatome. It is common in older patients and those with malignancy and in cranial nerves more than spinal nerves.
- **Disseminated herpes zoster** This is a serious disorder of the immunosuppressed. The condition begins as classical dermatomal herpes zoster, but vesicles continue to erupt all over the cutaneous surface (Fig. 14.42) as in chickenpox. Visceral, pulmonary, hepatic and neurological involvement may result and there is a significant mortality.
- **Trigeminal trophic syndrome** (Ch. 29) A neurotrophic ulceration (Fig. 14.43) usually in the elderly, secondary either to ablative treatment for trigeminal neuralgia or to damage to the trigeminal nerve or ganglion by herpes zoster (other causes include brain stem tumours, stroke or trauma). Negative pressure wound therapy may be effective.
- **Postherpetic neuralgia** This is a miserable condition that occurs mainly in the elderly and persists long after the cutaneous eruption has healed. It responds poorly to analgesics and psychotropic agents.

Management

HHV-3 can be identified under the electron microscope and also be grown on tissue culture. There are a number of treatments.

- **Aciclovir** Aciclovir, 800 mg five times daily for 1 week, is the treatment of choice for all forms of complicated herpes zoster. It may well be life saving in the disseminated variety and reduces the incidence of complications, although it does not appear to affect postherpetic neuralgia.
- **Other antiviral drugs** These are effective and may replace aciclovir because of aciclovir resistance or the need to be given less frequently. They are famciclovir, valaciclovir and foscarnet.
- **Systemic glucocorticosteroids** Prednisolone, 40–60 mg daily for 2 weeks and with a reduction over the next 3 weeks, has been given to reduce postinflammatory neuralgia in the elderly. Recent trials do not show any convincing evidence that this treatment is effective.
- **Topical therapy** Topical 5% aciclovir, applied five times daily.
- **Analgesia and bed rest** Analgesia is essential, although it is best to avoid opiates. The patient should be advised to rest.
- **Postherpetic neuralgia** Amitriptyline, carbamazepine, nortriptyline or gabapentin are worth trying. Capsaicin 0.025% topically has been reported as being helpful.
- **Vaccination** This may prevent shingles and post herpetic neuralgia.

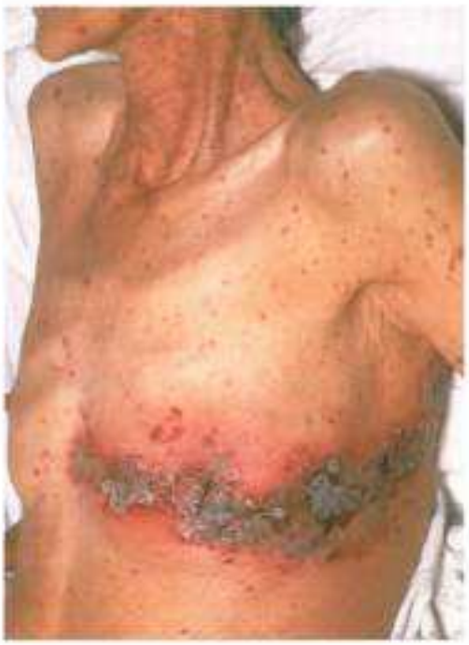


Fig. 14.42 Disseminated herpes zoster. In the immunosuppressed, the virus may disseminate to involve most of the cutaneous surface. (Courtesy of St Bartholomew's Hospital.)

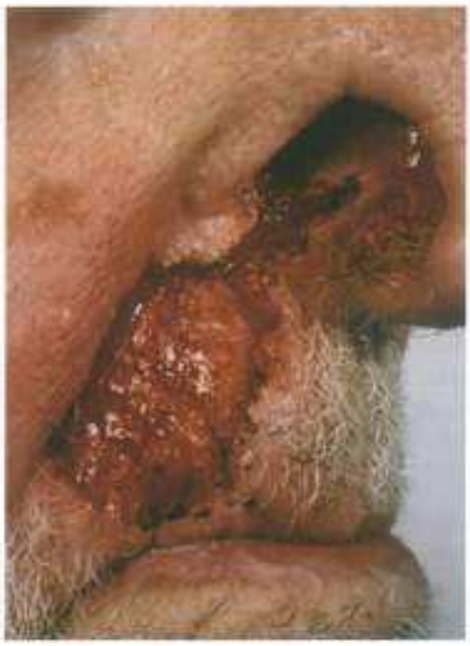


Fig. 14.43 Trigeminal trophic syndrome. This is a neutropic condition resulting in ulceration of the skin of the nose secondary to trauma, but resulting originally from trigeminal nerve damage from herpes zoster, ablative therapy and other neurological causes.

Infectious mononucleosis

Infectious mononucleosis is characterized by fever, sore throat with exudative tonsillitis, splenomegaly, lymphadenopathy and a lymphocytosis with atypical cells.

Aetiology

Infectious mononucleosis is caused by the Epstein–Barr virus (HHV-4). It infects oropharyngeal epithelial cells and B cells but is restricted by normal immune surveillance. It also causes the haemophagocytic syndrome and is implicated in Burkitt's lymphoma, nasopharyngeal carcinoma, post-transplant lymphoproliferative disorders, Hodgkin's disease, non-Hodgkin's lymphoma in patients with AIDS, and oral hairy leukoplakia.

Clinical Features

Symptoms

Patients present with fever and a sore throat and enlarged lymph nodes.

Morphology

Ten per cent get a maculopapular rash, which rises to 100% if ampicillin is prescribed for the sore throat. An enanthem of petechiae at the junction of the hard and soft palate occurs on the second or third day of fever. Unusual cutaneous complications include acute urticaria, a transient cold urticaria caused by cold agglutinins, which are quite common in infectious mononucleosis. Petechiae occur secondary to thrombocytopenic purpura. An hydroa vacciniforme-like eruption of vesiculopapules on the face, dorsum of the hands, forearms and legs, leaving destructive disfiguring scars not associated with light, has been described in patients in Asia and Mexico.

Management of Infectious Mononucleosis

The diagnosis is made by finding atypical lymphocytes on a blood film. The Paul Bunnell test is positive after 10 days and an IgM antibody to Epstein–Barr viral capsid antigen is present during the infection and persists for a few months. IgG antibody is present for life. Ampicillin is contraindicated (Fig. 14.44).

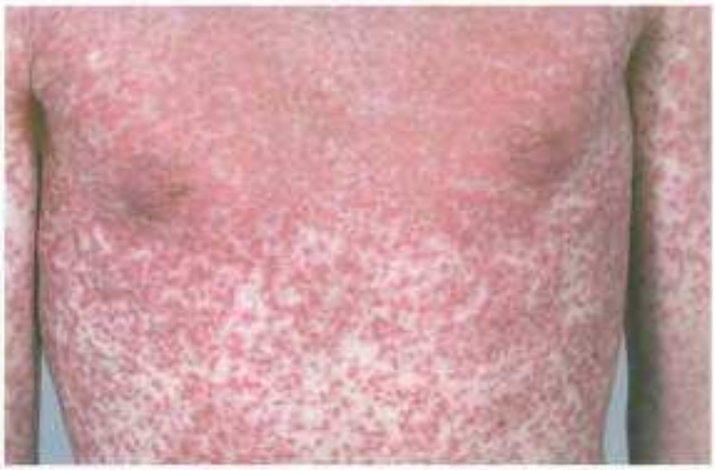


Fig. 14.44 Infectious mononucleosis. All patients who are prescribed ampicillin for the sore throat associated with infectious mononucleosis develop a widespread maculopapular rash.

Cytomegalovirus

Cytomegalovirus (HHV-5) may cause a mononucleosis-like syndrome and, more rarely, a blueberry muffin picture in infancy. It causes severe illness with cutaneous complications in the immunosuppressed.

Aetiology

Cytomegalovirus antibodies are present in 40–100% of the population, depending on the socioeconomic conditions. Cytomegalovirus usually causes an inapparent primary infection that is followed by lifelong carriage or intermittent shedding of the virus. It is an opportunist and leads to multiorgan involvement in the immunosuppressed, especially pneumonitis, gastroenteritis and retinitis. It may be transmitted sexually, via blood products, or by organ transplantation. The fetus is at risk from intrauterine infection and the infant perinatally by infected cervical secretions or neonatally via infected breast milk. It is a leading cause of mental retardation, blindness and deafness.

Clinical Features

The clinical features vary with the type of infection.

- **Localized cutaneous infection** It may arise on the skin from reactivation of latent virus or autoinoculation in periorificial areas by faecal, urinary or salivary shedding of CMV. It often occurs anogenitally after herpes simplex in HIV patients. Vesicles and ulcers form.
- **Congenital infection** This results in hepatosplenomegaly, jaundice, neurological damage and purpura. These infants often die. Blueberry muffin purple papules or nodules (Fig. 14.45) lasting 4–6 weeks are caused by erythropoietic tissue in the dermis derived from undifferentiated dermal mesenchyme.
- **Immunosuppression** Severe or fatal pneumonitis, hepatitis, retinitis and gastrointestinal ulceration may occur in the immunosuppressed, especially with AIDS or organ transplantation. There may be a widespread papular often purpuric eruption, vesiculo-bullous lesions (Fig. 14.46), indurated pigmented nodules or plaques or perianal, genital or buttock ulceration.
- **Normal healthy individuals** Cytomegalovirus mononucleosis can occur, with fever, lymphadenopathy, malaise and occasionally a follicular maculopapular rash lasting 48 hours; the rash becomes pronounced if ampicillin is given to treat the fever.

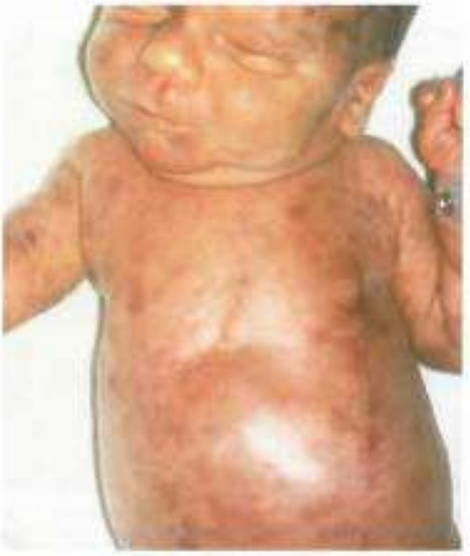


Fig. 14.45 Blueberry muffin nodules. There is erythropoietic tissue in the dermis derived from undifferentiated dermal mesenchyme. This may occur in congenital cytomegalovirus infection. (Courtesy of Dr David Atherton.)

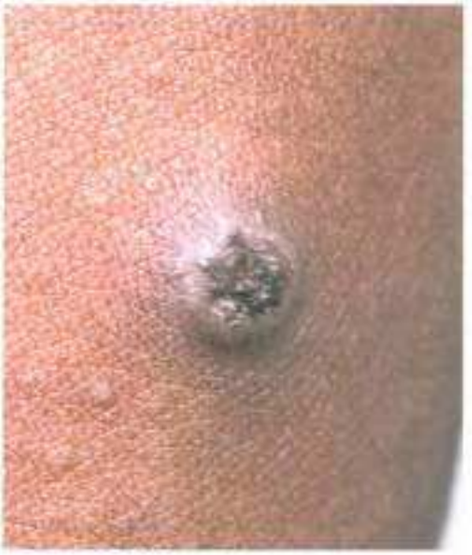


Fig. 14.46 Cytomegalovirus infection. A vesiculo-bullous haemorrhagic nodule is present in association with a papular rash in this woman with HIV infection. A viral swab for culture and a biopsy is necessary for diagnosis.

Management

The diagnosis may be established by isolating the virus from throat washings, urine, bronchoalveolar lavage fluid, blood and also biopsy material. Intranuclear eosinophilic 'owl's eye' inclusions surrounded by a clear halo, which sharply delineates it from the nuclear membrane can be found on biopsy of the skin. Specific CMV immunochemical tests and PCR are useful. Cytomegalovirus antibodies do develop. Ganciclovir and valganciclovir are usually effective, but foscarnet and cidofovir are indicated in resistant cases.

Variola (Smallpox) and vaccinia

Smallpox is an infection with a pox virus, which was commonly fatal. Vaccinia is the virus used to vaccinate against it.

Aetiology

The pox viruses are the largest animal viruses and can be seen under a light microscope. They are DNA viruses that replicate in the cytoplasm and are well adapted for epidermal cells. Smallpox was eradicated following mass vaccination programmes but the Center for Disease Control and Prevention in Atlanta, Georgia and the Russian State Research Centre of Virology and Biotechnology in Koltsova maintain viable variola and so, theoretically, there is the possibility of clandestine stockpiling of the virus for biological warfare. Vaccinia does not occur naturally but was developed by serial propagation; it is thought to be a mutant of either cowpox or variola. It was routinely used for smallpox vaccination and complications from its use were sometimes seen. It is now virtually restricted to military recruits.

Clinical Features

Symptoms

Smallpox presents as an influenza-like prodrome with a high fever, headache, backache and abdominal pain. This lasts 2–4 days following a 7–17 day incubation period.

Morphology

In 10% of Caucasians there is an initial erythematous exanthem that is followed by the appearance of macules, papules, vesicles and pustules, which are umbilicated (Fig. 14.47). These crust and subsequently scar. The sequence is synchronous.

There is a buccal and pharyngeal enanthem from which the virus is shed and transmitted.

Distribution

The rash is centrifugal beginning on the face, spreading to the forearms and hands and then to the lower limbs and trunk within a week.

Systemic features

Complications include blindness from panophthalmitis, arthritis and encephalitis. Death results from toxaemia and hypotensive shock.

Management

Smallpox is unlikely to be encountered but it has been contracted from a laboratory where the virus was housed. The diagnosis is made using PCR or electromicroscopically. There is no effective specific antiviral agent. Two different strains of variola are recognized. The virulent strain (variola major) was fatal in half the patients. The less virulent strain (variola minor; also known as *alastrim*) rarely caused death but was disfiguring.

Monkeypox, a pox virus infection from an arboreal squirrel reservoir in the tropical rainforests of Western and Central Africa, produces fever, respiratory symptoms and synchronized lesions just like smallpox but the patients are more prone to inguinal and cervical lymphadenopathy and the mortality is much lower.

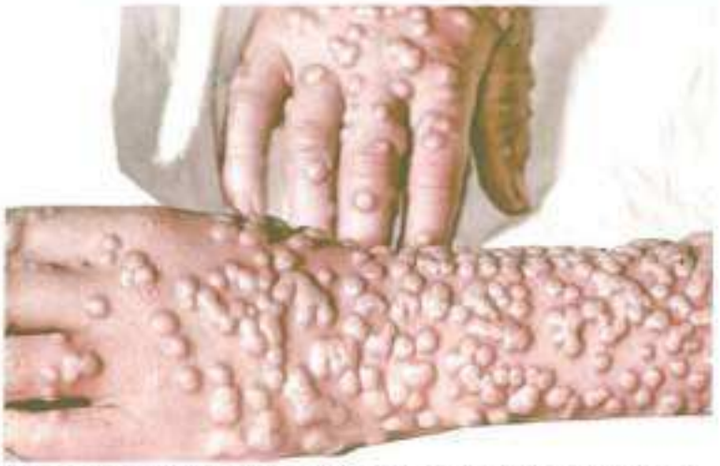


Fig. 14.47 Smallpox (alastrim). The vesicles are umbilicated and the evolution of lesions synchronous. The eruption is centrifugal, beginning on the face and finally appearing on the trunk.

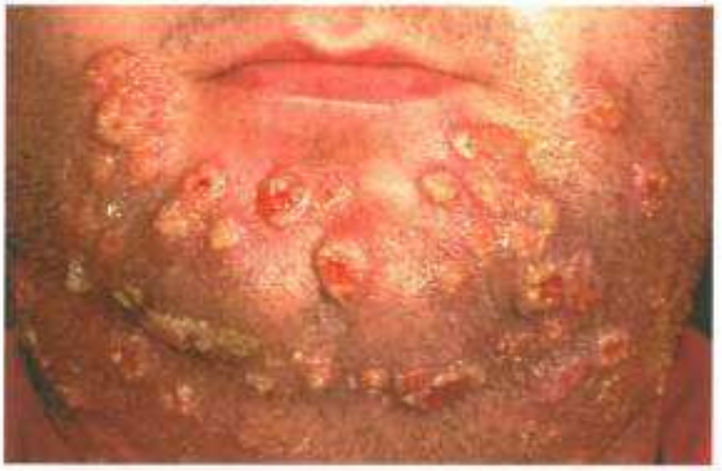


Fig. 14.48 Vaccinia. Accidental autoinoculation of the virus from a vaccination site results in umbilicated vesicles identical to those of the original vaccination.

Vaccinia

Complications of vaccination included:

- accidental autoinoculation from the vaccination site, which occasionally resulted in an eruption of umbilicated vesicles (Fig. 14.48) identical to those of the initial vaccination
- generalized vaccinia, usually the result of inappropriate vaccination of infants, atopics or the immunosuppressed
- bacterial sepsis of the vaccination site
- erythema multiforme
- encephalitis.

Molluscum contagiosum

A self-limiting mucocutaneous infection caused by a large DNA pox virus, resulting in distinctive umbilicated dome-shaped papules.

Aetiology

There are two types of molluscum contagiosum but at present these do not seem to be of any clinical significance. It is common in children and young adults. It is contracted from swimming pools, communal bathing facilities, close contact between children and sexually. The incubation period has been variably estimated at 2 weeks to 6 months. The virus is commonly associated with disorders of T cell function, particularly atopic dermatitis, congenital immunodeficiency, lymphoproliferative disorders and HIV infection. Atopics often have widespread infections if treated inappropriately with topical steroids.

Clinical Features

Symptoms

Asymptomatic spots on the skin.

Morphology

These are flesh-coloured dome-shaped papules with a central depression on their surface (Fig. 14.49). This 'umbilication' is the most important diagnostic sign. The papules vary from a millimetre to a centimetre in size. Multiple lesions are the norm (Fig. 14.50), but sometimes a solitary one occurs and the diagnosis will be missed. An individual lesion lasts about 2 months. As the lesion involutes, it may become inflamed or eczematous. The outbreak resolves spontaneously within a year. It rarely returns a second time, differing from the wart virus.

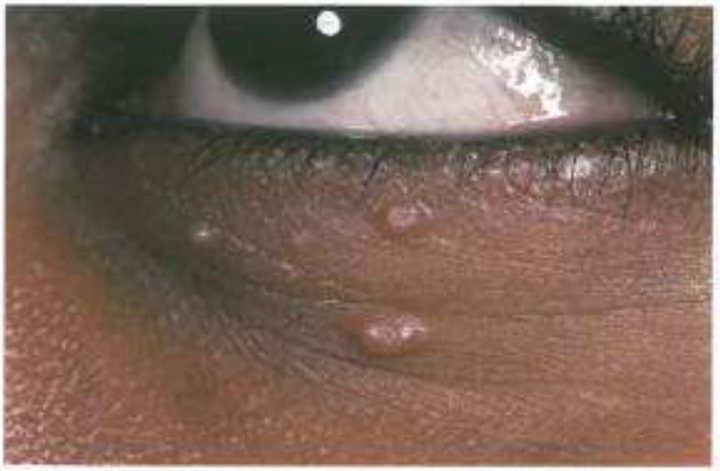


Fig. 14.49 Molluscum contagiosum. A central depression ('umbilication') is visible on the surface of the dome-shaped papules. In adults there may be underlying HIV infection, particularly on the face, as in this patient.

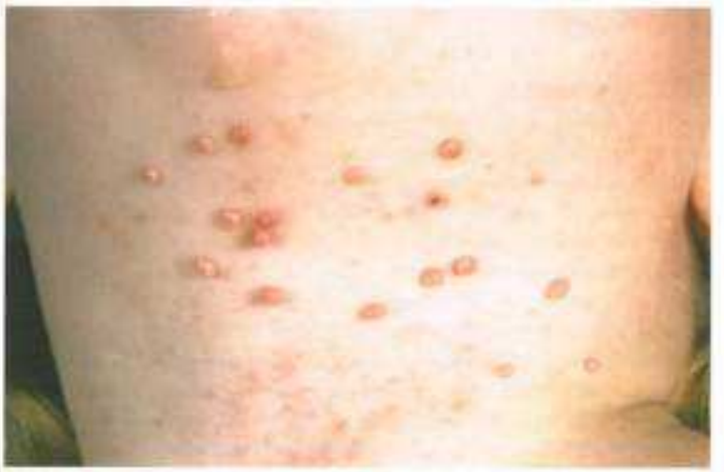


Fig. 14.50 Molluscа contagiosa. Several discrete dome-shaped papules are present on the neck of this 2-year-old girl. She also suffered from eczema.

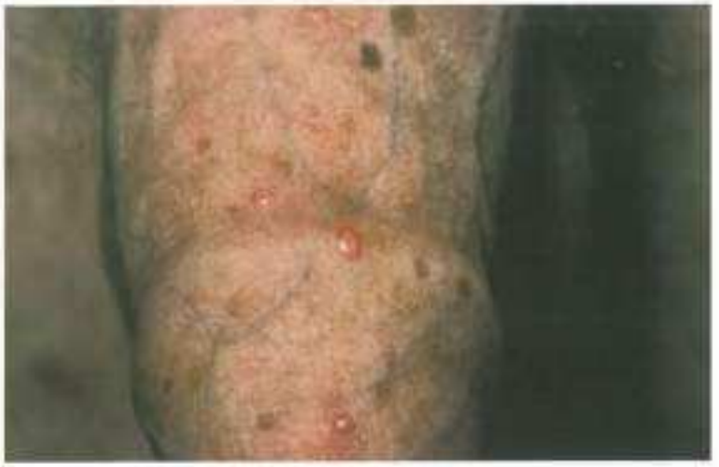


Fig. 14.51 Genital molluscum contagiosum. Molusca on the genitalis or in the pubic area or lower abdomen in adults are normaly contracted during sexual activity.

Fig. 14.52 Solitary molluscum contagiosum. Single 'giant' lesions may not be suspected clinically. Cytology or histopathology are diagnostic.

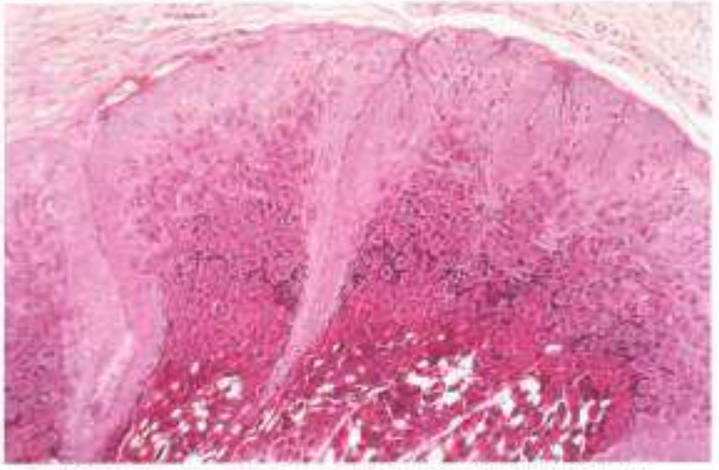


Fig. 14.53 Molluscum contagiosum. The cup-shaped invagination of the epidermis is typical. Intracytoplasmic inclusion bodies, which completely fill the cell and compress the nucleus, clinch the diagnosis.

Distribution

Anywhere, including the face and neck. Those occurring on the genitalia (Fig. 14.51) or lower abdomen in adults are almost invariably contracted during sexual activity. Those particularly on the face in adults are suggestive of HIV infection.

Management

Multiple lesions are easy to diagnose. Solitary lesions (Fig. 14.52) may not be suspected if the tell-tale depression in the surface of the lesion is not noticed; but the histology of a mass of homogenous, round bodies in the epidermis is characteristic (Fig. 14.53). These so-called mollusca bodies can also be observed under the microscope by squeezing the lesion onto a slide and adding potassium hydroxide.

Since the lesions are harmless and involute spontaneously, and treatment with liquid nitrogen is not appreciated by children, some doctors leave them alone. However, they remain a source of infection and many parents press for treatment. The application of nitrogen need only be momentary. It is usually pretty well tolerated if a rapport is established between the doctor and the patient first. Topical lidocaine cream (EMLA) is a useful anaesthetic if applied ½ hour before treatment.

In adults with genital lesions, liquid nitrogen is the treatment of choice; the patient and partners should also be screened for other sexually transmitted diseases.

Cidofovir is a nucleotide analogue with activity against a number of DNA viruses. It can be given systemically or topically as a 1–3% ointment. Imiquimod may also be effective.

Curettage and cautery is useful for a single lesion and is sometimes employed for widespread infections, particularly under general anaesthesia. This is rarely necessary.

Molluscum contagiosum was virtually impossible to treat in HIV-positive patients, but highly active antiretroviral therapy (HAART) including HIV-1 protease inhibitors and nucleoside analogue reverse transcriptase inhibitors has considerably improved therapy.

Orf (Ecthyma contagiosum)

A viral disorder of the skin contracted from infected sheep or goats.

Aetiology

Orf is caused by a parapox DNA virus that can survive for long periods on inanimate matter such as fences and feeding troughs. It infects particularly newborn lambs and goats, causing a pustular dermatosis around the mouth and nose ('scabby mouth'). It is an occupational hazard for farmers or veterinary surgeons. Feeding orphaned lambs from a bottle is a common mode of transmission. There is no human to human transmission and there is lifelong immunity after an infection.

Clinical Features

Symptoms

After an incubation of 3 to 7 days, a spot appears usually on the finger.

Morphology

Orf has various stages, which heal uneventfully in 35 days. It begins as a red papule (maculopapular stage) that proceeds to become a nodule, with a red centre, white middle and red periphery (target stage; Fig. 14.54). The surface begins to weep and then crust with black dots, followed by little papillomas (papillomatous stage) on its surface. The crust becomes very thick and subsequently falls off (regressive stage). Multiple lesions may be present (Fig. 14.55).

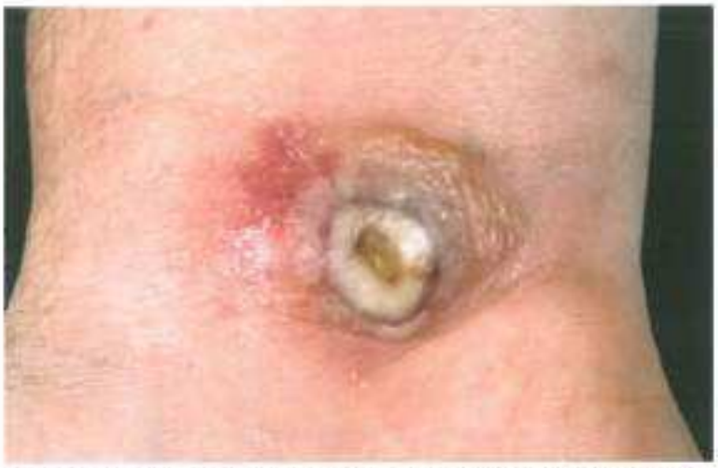


Fig. 14.54 Orf. The lesions are quite targetoid with different zones of coloration. The condition is contracted from infected lambs. Patients do not acquire immunity and may get recurrences.

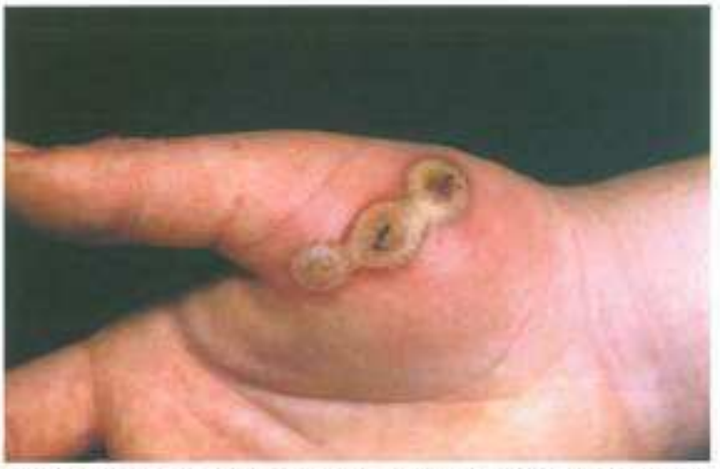


Fig. 14.55 Orf. The fingers or hand are the most common sites. Three lesions are present. It lasts 35 days. It may cause erythema multiforme. Butchers who process halal meat may be at risk.

Distribution

Orf occurs most commonly on the index finger.

Management

Regional lymphadenopathy, lymphangiitis and a short-lived fever are common. Toxic erythema or erythema multiforme occasionally accompanies the infection. Secondary bacterial infection may occur. The diagnosis is usually made clinically but can be established by electron microscopy, PCR or from biopsy material. Imiquimod may induce regression and systemic antibiotics may be required for secondary bacterial infection.

Warts

A common human papilloma virus (HPV) infection of the skin or mucous membranes.

Aetiology

HPV is a small (50–55 nm) icosahedral non-enveloped double-stranded DNA virus that causes squamous epithelial cell proliferation and warts. Animal papilloma viruses exist but are host specific. The virus cannot be grown in tissue culture because it requires differentiated squamous epithelium for gene expression. The incubation period is not exactly known, but an average of 4 months (range 1–20 months) has been calculated. HPV commonly affects children and young adults, the maximum incidence being between 12 and 16 years of age. The incidence is about 10% in youth. Warts occur worldwide and the incidence is rising, accounting for 10–25% of dermatological outpatient attendances.

Modern investigational techniques, especially DNA hybridization, have confirmed that there are many types of HPV. Common mosaic warts are mostly HPV-2, plane warts HPV-3, and deeply inwardly growing warts of the palms and soles HPV-1. Genital warts are types 6, 10, 11, 16 and 18. HPV-2 has been isolated in a few genital warts, which indicates that warts can be transferred from the hands. Genital warts may become quite exuberant, hyperplastic and cauliflower-like, especially during pregnancy. Many regress after parturition. Some wart viruses are potentially oncogenic in animals and malignant transformation in the cervix, vulva and penis is associated with HPV-16 and HPV-18. The other types are not oncogenic, except for HPV-5 which is associated with *epidermodysplasia verruciformis*. This is a rare autosomal recessive (occasionally autosomal dominant) inherited disorder of widespread and persistent infection with the HPV virus, secondary usually to impaired cell-mediated immunity with reduction in T cell numbers and function. There are mutations in EVER1 and EVER 2. Clinically, the warts simulate plane warts or pityriasis versicolor or may be reddish plaques. They are numerous and develop rapidly in childhood on the face, neck, backs of the hands, feet and elsewhere and may become generalized. Dysplasia or malignancy may develop, particularly Bowen's disease, actinic keratoses and squamous cell carcinomas, especially on exposed skin and so sunlight may act as a co-carcinogen.

Infectivity depends on the viral load and host immunity. Cell-mediated immunity is most important. Warts may be florid in those with lymphoma, AIDS or renal transplants.

Extensive warts occur in certain syndromes:

- Wiskott–Aldrich syndrome
- X-linked hyper IgM immunodeficiency
- Netherton's syndrome
- Klinefelter's syndrome
- Clouston syndrome
- Idiopathic CD4 deficiency. Tuberculosis and VZV are common as well
- WHIM syndrome (Warts, Hypogammaglobulinaemia, Immunodeficiency, Myelokathesis [retention of mature neutrophils in the bone marrow]). These patients suffer recurrent bacterial infections from infancy (pneumonia, cellulitis and abscesses). Viral immunity is generally good except for the susceptibility to mucocutaneous warts. It was the first human disease ascribed to abnormal chemokine signalling. There is a heterogeneous mutation of the chemokine receptor on CXCR4 gene on chromosome 2q21.

Humoral immunity appears to be less important and warts are uncommon in multiple myeloma. Previous infection does not convey permanent immunity nor does one type of wart virus convey immunity against another.

Warts are contagious and spread more easily if there is local trauma (they are, therefore, more common on the hands, feet and knees). They are commonly contracted from institutions where there are communal bathing and changing facilities, such as hotel bedrooms, bathrooms and swimming pools. Anogenital warts are contracted sexually. Children with genital warts present a special problem for occasionally they may be secondary to sexual abuse, but more often they are caused by autoinoculation or are transmitted in bath water. Vertical infection may occur from mother to infant following delivery through an infected birth canal.

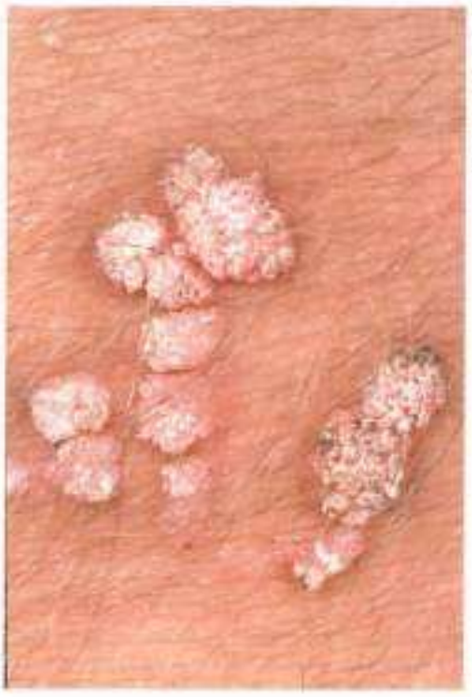


Fig. 14.56 Common warts. The hands and fingers are the most common sites. The lesions are discrete, firm papules with a rough surface.

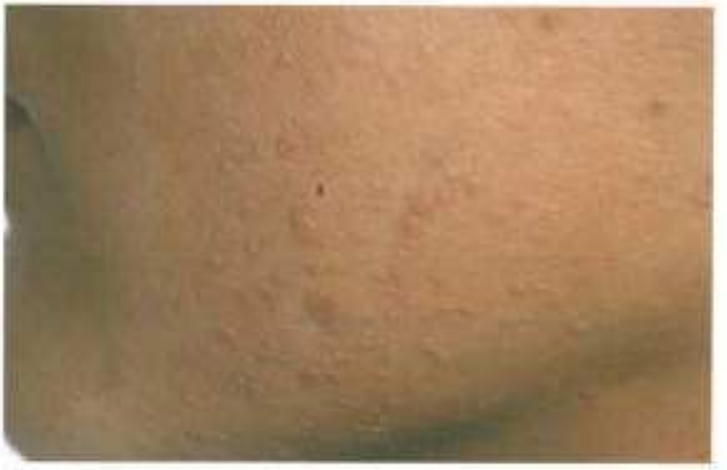


Fig. 14.57 Plane warts. The lesions are well-defined, flat-topped, flesh-coloured or pigmented papules. They may be misdiagnosed on the face as acne. They are treated with gentle cryotherapy, but may be quite persistent.

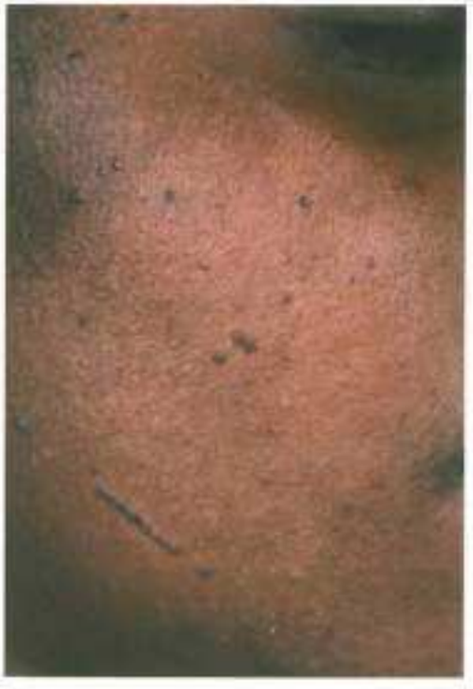


Fig. 14.58 Plane warts. There are a number of pigmented flat-topped papules and in one area, a linear collection of them. Plane warts are one of the causes of Koebner phenomenon.

Clinical Features of Common Warts

Symptoms

Common warts are asymptomatic but unsightly.

Morphology

Warts are discrete, flesh-coloured papules with a rough surface (Fig. 14.56). They may be single or multiple and occasionally can be quite large.

Distribution

Common warts can occur anywhere but especially on hands and feet.

Clinical Features of Plane Warts

Symptoms

Flat spots on the skin.

Morphology

It is a flesh-coloured or pigmented, very slightly raised, well-defined, flat-topped lesion (Fig. 14.57). It has a smooth or very slightly roughened surface. Plane warts often occur in lines corresponding to a scratch (Fig. 14.58) or other such trauma (the Koebner phenomenon).

Distribution

They can occur anywhere, but particularly on the face, hands and limbs. They are frequently misdiagnosed, especially on the face, where they are liable to be treated with topical steroids, in which case they spread. They may be peculiarly persistent and account for about 3% of warts.

Clinical Features of Verrucae

Symptoms

Verrucae (plantar warts) may be quite painful and can interfere with walking.

Morphology

They are discrete, only just raised and have a roughened surface.

Distribution

They can occur on the palm but more usually on the sole, where they penetrate deeply because of the pressure of body weight. Deep plantar warts are sometimes known as *myrmacia* (ant hill). If they are pared with a scalpel, minute bleeding points are apparent, and this helps to differentiate a verruca from a corn (in which the skin becomes more and more normal in appearance as it is pared). As warts involute, minute haemorrhages occur within them as a result of thrombosed capillaries.

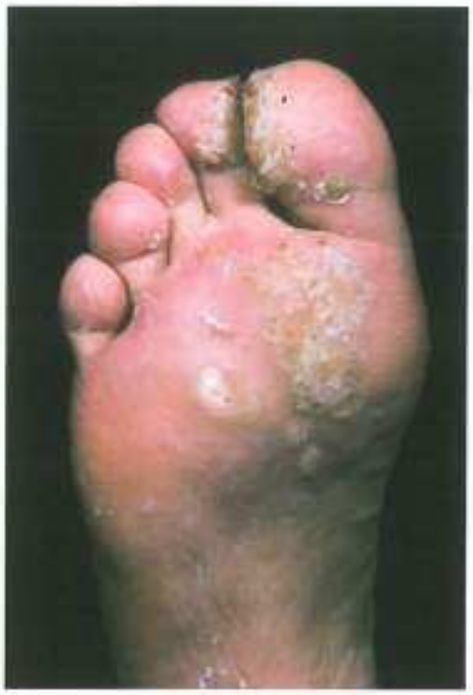


Fig. 14.59 Mosaic warts. These are especially difficult to treat. The individual warts are discernible within the plaques of rough skin.

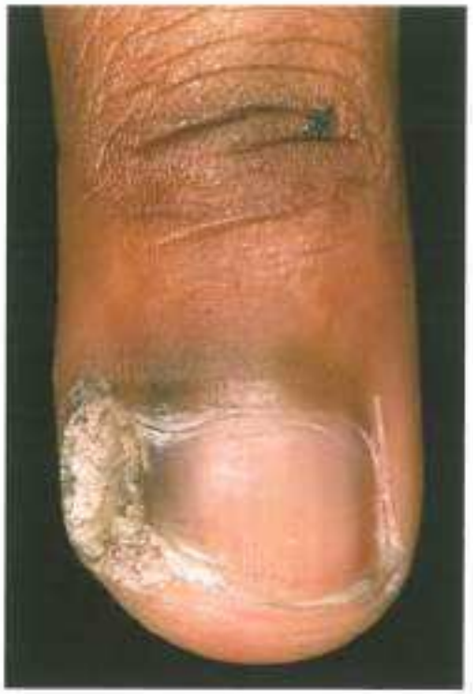


Fig. 14.60 Periungual warts. These may be quite persistent and cryotherapy is painful.

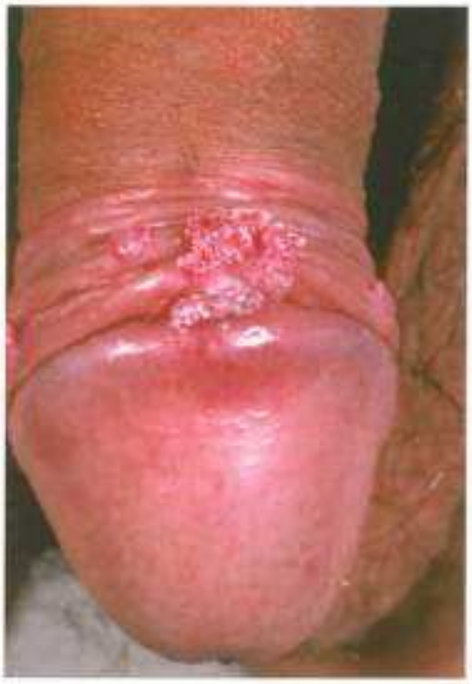


Fig. 14.61 Penile warts. Filiform warts on the genitalia are usually sexually transmitted and the patient should be screened for other such disorders.

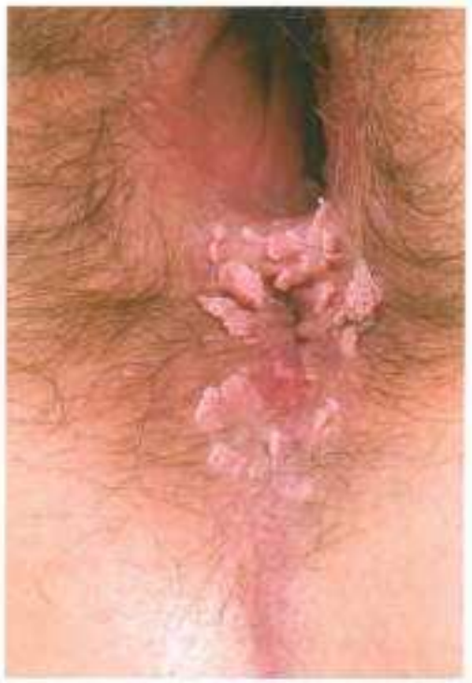


Fig. 14.62 Anogenital warts. Soft, filiform, pink pedunculated lesions are present.

Clinical Features of Mosaic Warts

Symptoms

Usually asymptomatic (unlike corns, which are painful).

Morphology

Plaques of roughened skin (Fig. 14.59) within which are delineated individual warts.

Distribution

Mosaic warts occur on the soles, heels, palmar surfaces and around the nails (Fig. 14.60). They last a long time and are particularly resistant to therapy, especially if associated with hyperhidrosis. It may be necessary to apply 5% acetic acid and to use magnification to see the extent of them. Patients often have a tendency to cold feet.

Clinical Features of Anogenital Warts

Symptoms

Anogenital warts are usually asymptomatic.

Morphology

There are three clinical forms of anogenital wart:

- the cauliflower-like type (condyloma acuminata)
- soft pink filiform (Fig. 14.61) often pedunculated sessile papules with a rough surface (Fig. 14.62)
- the well-defined and keratotic wart, simulating verruca vulgaris.

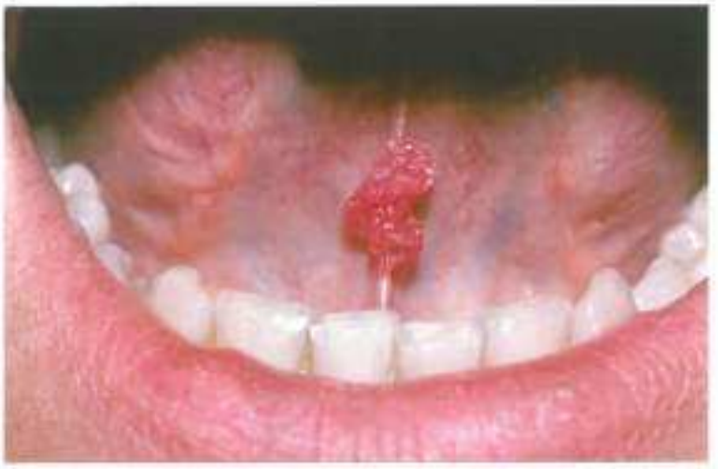


Fig. 14.63 Orogenital warts. Warts may occur on mucous membranes. This wart was probably contracted sexually.

Distribution

Anogenital warts occur on the penis, scrotum, inguinal folds, pubic area, vulva and anus. They may also occur within the urethra and vagina, on the cervix and within the anal canal. Anogenital warts may spread to the face and mouth (Fig. 14.63) from orogenital contact and in children (Fig. 14.64), although sexual abuse has to be considered, the distribution away from the anus or vulva usually points to maternal infection at birth.

The *Buschke–Löwenstein giant condyloma acuminatum* is a rare genital perianal HPV infection, which exhibits malignant behaviour contrasting with its benign histological features. Recurrences are common and there is a risk of transformation into a fully invasive squamous cell carcinoma.

Pearly penile papules (Ch. 9) are sometimes mistaken for warts. They are a normal variant occurring on the corona and are thought to be angiofibromas.

Fig. 14.64 Perianal warts. Although sexual abuse has to be considered in a child (this one was 3 years old), they are usually contracted during labour from maternal infection in and around the birth canal.

Management

Topical steroids are sometimes misprescribed, either for plane warts when the diagnosis has been missed or for anal warts when the area has not been examined. Viral warts are uncommon after middle-age, when the diagnosis is more likely to be a seborrhoeic wart or a squamous cell carcinoma, or may be the result of immunosuppression. Occasionally, warts become secondarily infected and painful. Release of the pus with a scalpel relieves the pain immediately. Resolution of the warts often follows.

Warts involute spontaneously: 35% have gone within 6 months, 55% within the year and 65% within 2 years. However, the response to treatment does decline with the increasing duration of the wart. Conservative treatment is often the wisest course, particularly in children. It is unfair to put children through painful procedures such as liquid nitrogen therapy. Most warts need at least 3 months of treatment, so patients must be dedicated. A wart may be pronounced cured when the normal skin creases are restored. Therapy resolves around physical (surgery, electrosurgery, cryosurgery and lasers), chemical (various acids), chemotherapy (podophyllin, 5-fluorouracil and bleomycin) and certain more experimental measures (immunotherapy, interferon and retinoids).

Common plane and mosaic warts

- **Topical remedies** Salicylic acid alone or in combination with lactic acid, podophyllin, glutaraldehyde and formaldehyde are all useful keratolytics. Formalin is often used for mosaic warts in a 3–10% solution as a soak. It is put into a saucer. The patient applies a fine film of vaseline around the verruca to protect the normal skin and then soaks it in the formalin for 10 minutes daily. It should be noted that formalin is a desiccant and may dry out the skin, particularly on the heel. Occasionally allergic contact dermatitis does occur, which in itself may be helpful. Indeed, contact allergens, such as dinitrochlorobenzene or diphencyprone, have been used to treat stubborn warts successfully.
- **Liquid nitrogen** This is usually effective for common warts, although somewhat uncomfortable. Liquid nitrogen causes an inflammatory response after an application of 15 seconds. Erythema results around the wart and subsequently oedema underneath it, which ideally will result in blistering. The wart usually falls off within 2 weeks, as the blister breaks. If the lesion is overtreated, haemorrhage into the blister sometimes occurs (blood blister). This is very painful, but instantaneous relief is achieved by using a scalpel to make a small nick in the blister, thus allowing release of the tension. A single application may be successful, but often a repeat course of treatment with longer application times is necessary.

  Plane warts require brief and accurate cryotherapy. It is often effective but postinflammatory hyperpigmentation is a risk.

  For verrucae applications have to be longer (30–60 seconds) than for hand warts because the verruca is so deep. The treatment is painful, particularly shortly afterwards, as the cryotherapy causes erythema, oedema, blistering and haemorrhage. The application should be repeated every 3 weeks and the patient can use a keratolytic in the meantime. Several treatments are required. Overzealous treatment can result in the recurrence of the wart around the site of the blister.
- **Cautery** If liquid nitrogen is unavailable, cautery may be used, but this may require a local anaesthetic, which limits its usefulness. Use of a hyfrecator is an alternative.
- **Surgery** Although surgery is contraindicated for multiple lesions, the best treatment for a single lesion is surgery. Administration of the local anaesthetic is painful (although somewhat reduced by topical lidocaine) but a general anaesthetic is rarely warranted. A fine incision is made around the border of the verruca with a scalpel, allowing access to and purchase for the curette. The wart is scraped away, the bleeding base is cauterized and then curetted once more before final cauterization. No sutures are required, the procedure only takes 5 minutes and the wound heals within 2–3 weeks. The patient must be forewarned that the area may be uncomfortable for a few days.

Anogenital warts

Genital warts are spread sexually and patients should be examined and investigated for other sexually transmissible diseases as well. Proctoscopy is indicated in patients with anal warts and a speculum examination and cervical smear is important in females. Patients are best referred to a genitourinary clinic.

- **Podophyllum resin** This cytotoxic resin has to be used with care because it is irritant to normal skin. A protective film of vaseline around the warts prior to the use of podophyllin is recommended. Podophyllin should not be used in pregnancy or for large masses of vascular warts since the drug is toxic and may be absorbed. It is not sensible either to use it on the hands of children, even in combination with salicyclic acid, since they might ingest the material. It has been suggested that it is a carcinogen, which is of some concern since HPV-16 and HPV-18 are potentially oncogenic and the two could act together as co-carcinogens.
- **Trichloracetic acid** If podophyllum resin is contraindicated or has failed, trichloracetic acid (50%) applied once every 2 weeks may be tried. It does not need to be washed off. If it is accidentally spilt onto normal skin it can be neutralized by sodium bicarbonate.
- **Surgery** Genital warts may be profuse, especially around the anus. Thomson's strip technique may be used. The warts are infiltrated with a solution of lidocaine with 1:300 000 epinephrine (adrenaline) and normal saline. The swelling permits the warts to be visualized individually, allowing them to be snipped away with scissors; bleeding is controlled with light diathermy (in order to avoid scarring).
- **Liquid nitrogen therapy** This is usually the treatment of choice.
- **Imiquimod** Imiquimod is an interferon immune enhancer. It can be used topically and has all the benefits of interferon without its limitations and has been used to treat persistent warts in HIV disease.

Experimental methods

Warts of all varieties can be remarkably frustrating to treat, particularly in the immunosuppressed (Figs 14.65 and 14.66). Sometimes experimental methods are used.

- **Bleomycin** A 1% solution of bleomycin may be injected into the warts, particularly those of the hands and feet. It may be necessary to anaesthetize the area because it is painful. An alternative technique is to apply the solution to the wart and inoculate it with a sharp blade.
- **Immunotherapy** Sensitizers of the skin, such as dinitrocholorobenzene or diphencyprone, are used to induce a delayed hypersensitivity contact dermatitis by applying the chemical to a site such as the outer upper arm. Once the patient has sensitized to the second application, then solutions are applied to the warts to induce a minor form of dermatitis. This can be very effective in chronic warts.

Corns and callosities

A corn is a localized hyperkeratosis of the skin (callosity) induced by repeated trauma. Corns and callosities are not a virus disorder of the skin. They are described here because the diagnosis of plantar warts and corns on the soles of the feet is sometimes confused.

Aetiology

Corns are localized callosities on the soles of the foot. Callosities are a response of the skin to continual rubbing and friction. Histologically, they consist of hyperkeratosis. They may be self-induced by children or anxious adults who pick or gnaw away at the skin on the side of a knuckle or finger as part of a habit tic. They may be occupational, such as those seen on the hands in manual workers. Most commonly, they occur on the feet, caused by ill-fitting footwear, deformed feet or both.

Clinical Features

A corn is a localized, tender, thickened area of skin with a central core over a bony prominence (Fig. 14.66), usually the metatarsal phalangeal joint. It may be differentiated from a verruca by paring the skin. This becomes more and more normal in appearance in a corn whereas tiny bleeding points result when a wart is pared. Corns are tender on direct pressure but not when squeezed between the finger and thumb. Exactly the opposite applies with a wart.

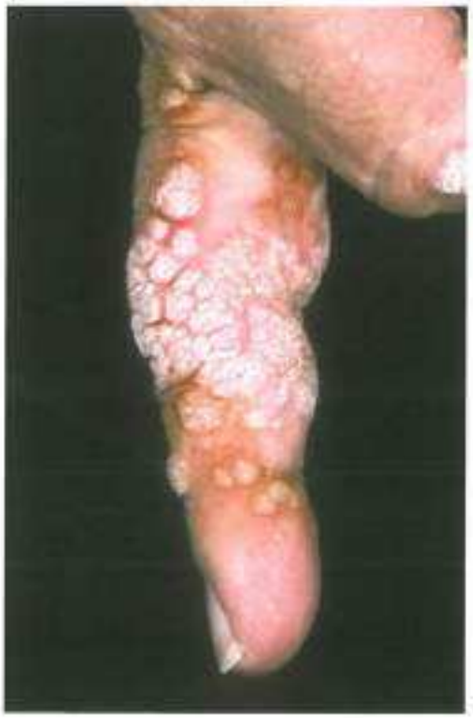


Fig. 14.65 Disseminated warts. Gross involvement with warts usually suggests immunosuppression. This patient had had a renal transplant and was on long-term antirejection, immunosuppressive agents.

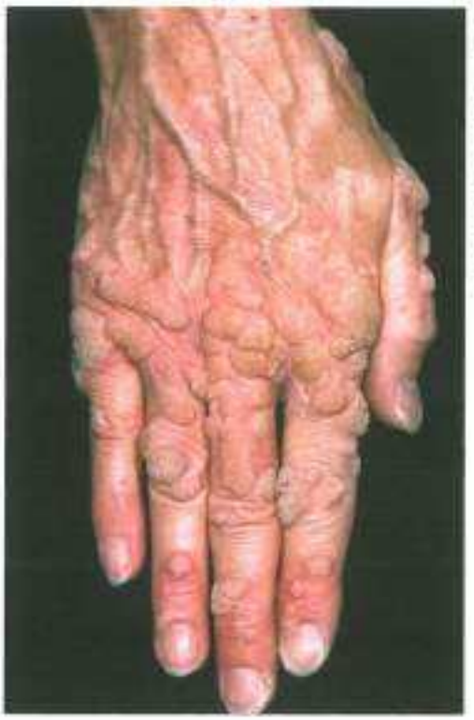


Fig. 14.66 Disseminated warts. This lady presented to her dermatologist with these warts. She was found to be lymphopenic. A request for a bone marrow biopsy, although greeted with scepticism, was granted. She was found to have non-Hodgkin's lymphoma.

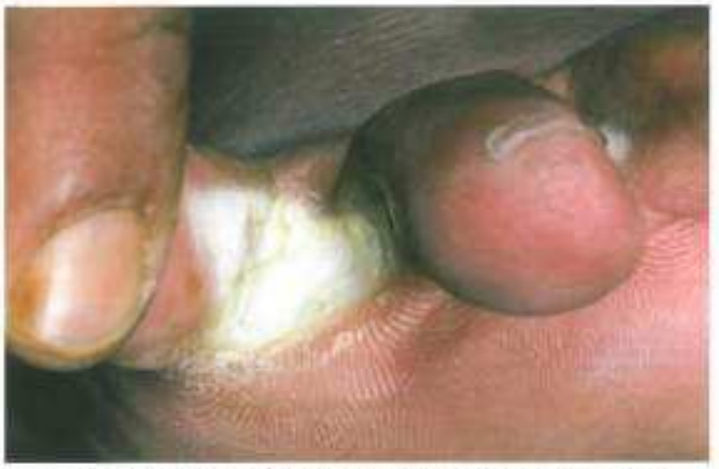


Fig. 14.67 Soft corn. Friction caused by tight-fitting shoes has resulted in a macerated corn between the fourth and fifth toes.

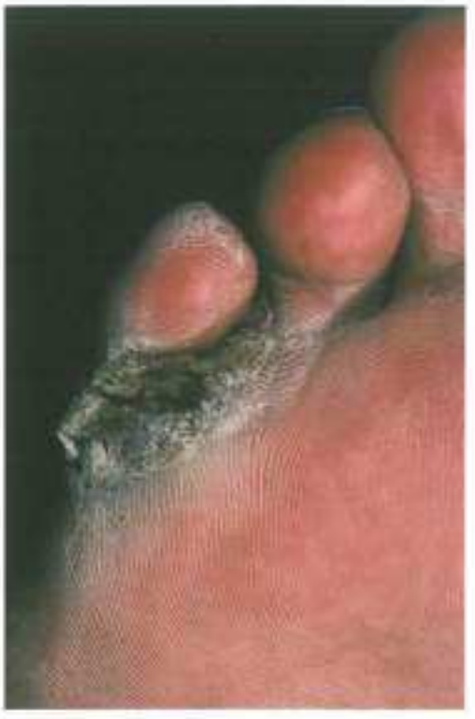


Fig. 14.68 Warts. Warts in and around the toes do not have the white macerated sodden appearance of the soft corn.

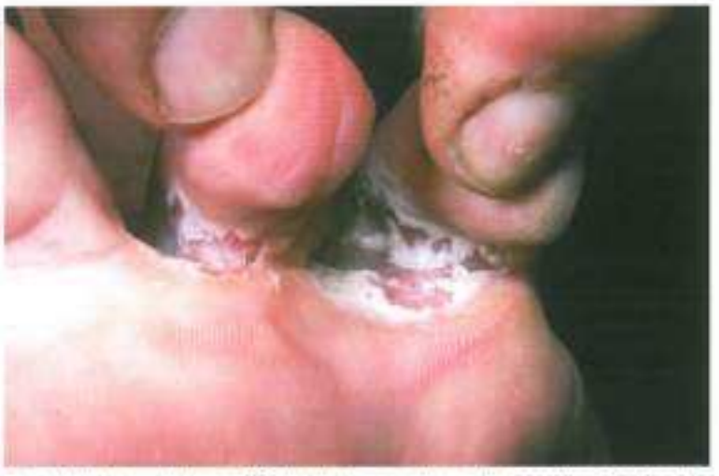


Fig. 14.69 Hyperhidrosis. This leads to maceration and secondary infection with fungi (tinea or candida) and/or bacteria (especially pseudomonas). In a soft corn the skin of the medial side of the fifth toe, although white, is quite thickened.

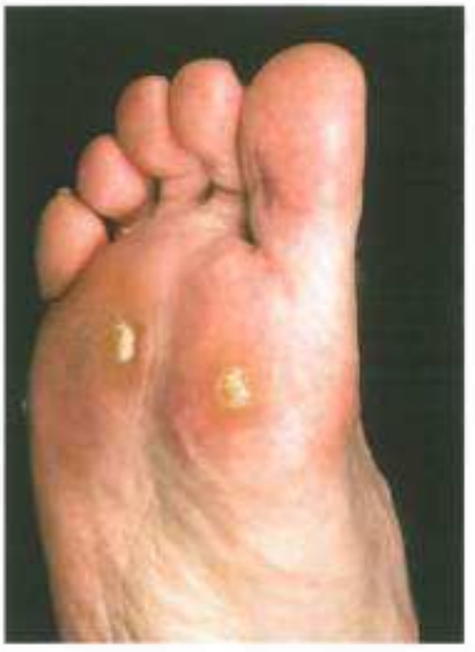


Fig. 14.70 Corns. Localized thickening of the skin is caused by friction from ill-fitting footwear and there is surrounding hyperkeratosis.

Callosities are a more diffuse thickening of the skin. They too may occur on the feet as a result of deformity and poor-fitting shoes. They may, however, occur anywhere on the skin as a result of friction.

A *soft corn* (Fig. 14.67) is the term used to describe the appearance of a callosity occurring on the medial aspect of the fifth toe and is the result of friction between that toe and its neighbour in tight-fitting shoes. Because of the occlusion, the skin becomes macerated and white. It is often misdiagnosed either as:

- Warts (Fig. 14.68) or
- Fungus (Fig. 14.69).

Management

Corns (Fig. 14.70) and callosities are best managed by chiropodists. Attention to footwear and the use of metatarsal foot supports are important. The corns themselves can be treated by salicyclic acid plasters, paring and sometimes by excision and curettage.

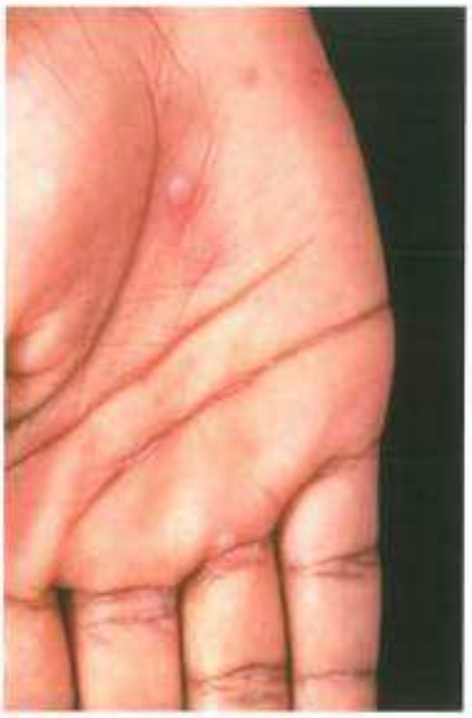


Fig. 14.71 Hand, foot and mouth disease. It is caused by a Coxsackievirus (usually A16) and occurs in epidemics. It is highly contagious.

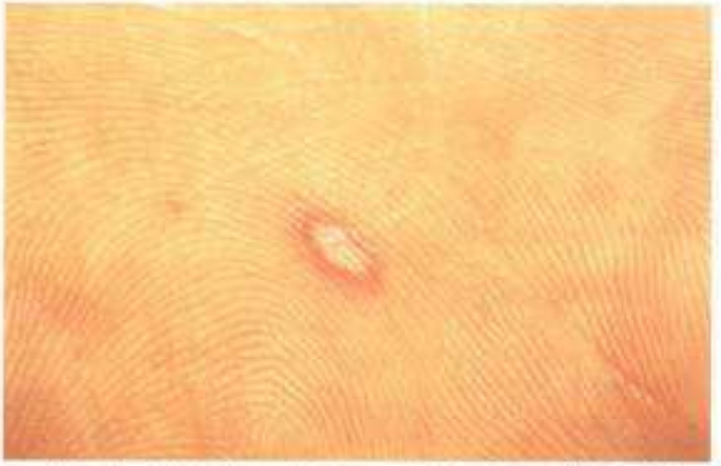


Fig. 14.72 Hand, foot and mouth disease. The lesion is an oval white vesicle surrounded by erythema on the palm. There are usually only a few lesions. (Courtesy of St Bartholomew's Hospital.)

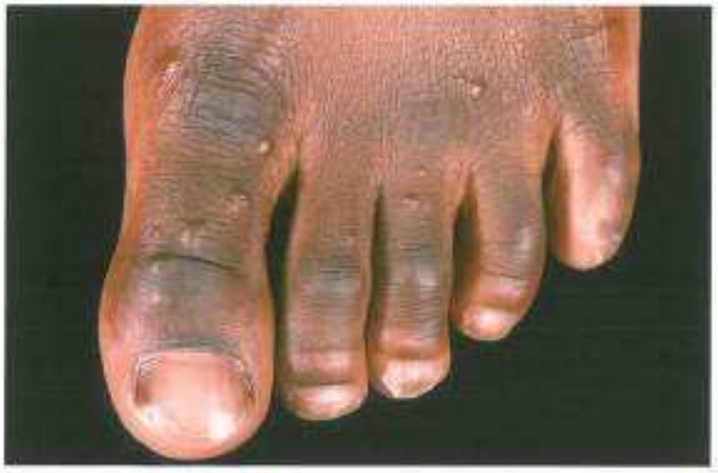


Fig. 14.73 Hand, foot and mouth disease. Sometimes there are many vesicles scattered over the hands and feet.

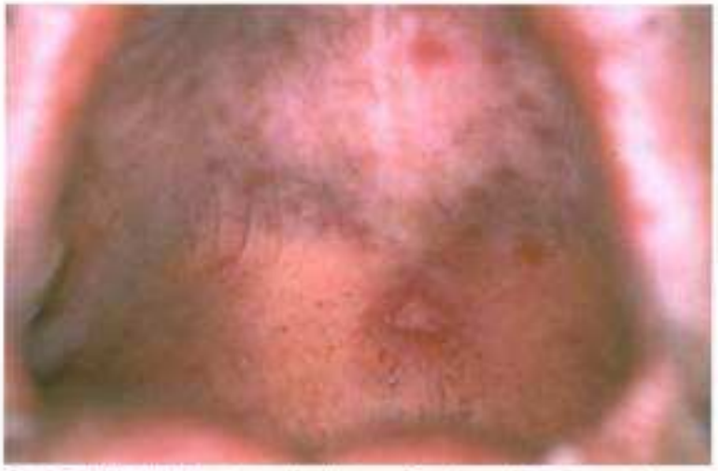


Fig. 14.74 Hand, foot and mouth disease. Discrete, small oval or round erosions occur in the mouth. The disorder is self-limiting and caused by a Coxsackievirus. (Courtesy of Dr Elisabeth Higgins.)

Hand, foot and mouth disease

A short-lived Coxsackievirus infection, which results in vesicles on the hands and feet and in an erosive stomatitis.

Aetiology

The condition occurs in epidemics and is caused by a Coxsackievirus (usually A16 strain). It enters via the buccal mucosa and small intestine and travels to regional lymph nodes; a viraemia ensues. It is usually seen in childhood but occasionally occurs in adults in institutions. It is highly contagious and spreads by droplet infection. It is quite benign. However, an enterovirus 71 infection may cause a serious illness of pneumonitis, myocarditis and neurological complications.

Clinical Features

Symptoms

There may be a mild prodrome of systemic disturbance during an incubation period of 5–7 days before the onset of the rash (Fig. 14.71).

Morphology

Oval slightly yellow vesicles surrounded by erythema (Fig. 14.72).

Distribution

The vesicles are sparsely distributed on the hands and feet but may occasionally be more extensive (Fig. 14.73). In the mouth (tongue, buccal mucosa, palate uvula and anterior tonsillar pillars; Fig. 14.74), the vesicles break easily and erosions result. They are larger and fewer in number than in herpangina (see below), which they otherwise resemble.

Management

There is no specific remedy. Hand, foot and mouth disease lasts 7 days and rarely recurs. The diagnosis may be confirmed by virus culture or PCR of throat, stool or vesicle swabs or serologically with specific enteroviral IgM (although this does not give rapid results).

Herpangina

A feverish illness associated with sore throat and dysphagia and a stomatitis: it is caused by a group A and B Coxsackievirus and also echoviruses.

Aetiology

Herpangina occurs mainly in children but can occur in adults, often in epidemic forms in the summer and autumn.

Clinical Features

Symptoms

There is an abrupt onset of fever lasting 4 or 5 days with a sore throat and difficulty swallowing.

Morphology

Usually 15–20 minute vesicles with a vivid red areola occur in the mouth; these become ulcers and heal within 5 to 7 days.

Distribution

The lesions of herpangina are seen on the pharynx, tonsils, pillars of the fauces, uvula and soft palate.

Management

The virus can be isolated from stool, vesicle fluid or nasopharynx and grown in tissue culture or in newborn mice just like other Coxsackievirus A strains, but PCR is the routine test nowadays. Electron microscopy may be positive. There is no specific treatment, and explanation and symptomatic measures should be sufficient.

Human immunodeficiency virus

HIV has a predilection for helper T and other cells, resulting in an increasing defect in cell-mediated immunity. This eventually leads to AIDS, which is characterized by opportunistic infections and malignancies. HIV is transmitted sexually, via blood products or vertically from mother to child.

Aetiology

HIV is an enveloped RNA retrovirus; there are two forms identified, HIV-1 and HIV-2, plus numerous strains. HIV-2 is most common in Africa. HIV has a predilection for $CD4^+$ T helper cells, monocytes and Langerhans' cells. These cells are gradually destroyed, interfering with non-specific host resistance such as phagocytosis by neutrophils and monocytes, natural killer cells and complement. Initially $CD8^+$ (suppressor/cytotoxic) T cell levels are raised and kill the virally infected target or tumour cells but as it progresses the $CD4^+$ cells are suppressed. The insidious immunological dysregulation leads to an increased number of opportunist infections and neoplastic disorders.

The mechanism of entry of the virus is as follows. The viral envelope fuses with the plasma membrane of the $CD4^+$ lymphocyte and the virus is internalized. The RNA genome is released into the cytoplasm and transcribed by reverse transcriptase to produce a DNA copy of the HIV RNA, which is integrated into the host DNA and expressed as a cellular gene. This viral DNA is transcribed back into RNA either to become new viral particles or to be translated into viral proteins, which are cleaved by proteases into viral structures, resulting in intact viruses that destroy the CD4 cells. The highly active antiretroviral (HAART) drugs act at various different sites in this process, i.e. entry/fusion (nucleoside and non-nucleoside reverse transcriptase inhibitors), integrase and protease inhibitors. These have turned HIV from a mortal illness to a chronic one with proportionately less serious opportunistic infections and Kaposi's sarcoma, but increased neoplasia, side-effects from the drugs and recognition of an immune reconstitution syndrome. In sub-Saharan Africa, however, HIV continues to have a disastrous effect.

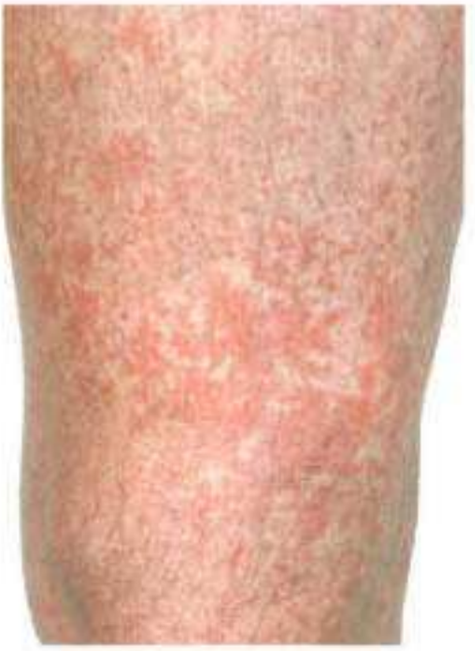


Fig. 14.75 Acute retroviral syndrome. A macular erythema is associated with an acute debilitating febrile illness.

HIV is detected initially by seroconversion, which can occur years before the appearance of clinical manifestations. It is also detected by identifying virus-specific proteins (core protein p24 and envelope glycoproteins gp41 for HIV-1 and gp36 for HIV-2). There is an initial phase of viraemia, often accompanied by an influenza-like illness. This is then followed by a period of clinical latency when the individual is HIV seropositive but viral particles are not detected in the blood. As the immune system breaks down, so the levels of $CD4^+$ cells fall, viraemia increases and AIDS occurs.

HIV infection and AIDS occurs worldwide and has become a major problem in Africa. Originally common in homosexual and bisexual men, infections in heterosexuals now account for over half of new cases. It also occurs in prostitutes, intravenous drug addicts, haemophiliacs (via contaminated blood) and the children and sexual partners of affected persons. It may be as long as 10 years before an individual develops the clinical symptoms of AIDS. This period has been greatly extended by the availability of HAART, but therapy itself has considerable side-effects.

The stage of HIV infection has been classified according to both the $CD4^+$ cell count and the occurrence of AIDS-defining illnesses, many of which are opportunistic.

Clinical Features

Untreated, it has a dynamic course leading from the initial infection to full-blown AIDS and death. It has been classified as follows:

- **Group I** About 50% of those infected have an initial glandular fever-like illness lasting 8 days, with fever, night sweats, malaise, myalgia, arthralgia, pharyngitis, tender lymphadenopathy, anorexia, vomiting and photophobia. One week later a macular rash (Fig. 14.75) appears on the face, neck and trunk that lasts 3–4 days. This illness occurs a few weeks after infection and is known as the *acute retroviral syndrome*. It coincides with the period of viraemia but patients can also be asymptomatic.
- **Group II** This covers the period when patients are asymptomatic but HIV positive. There may, however, be suppression of T helper cells, thrombocytopenia and leucopenia and early neurological dysfunction towards the end of this stage.
- **Group III** In this group, there is persistent generalized lymphadenopathy.

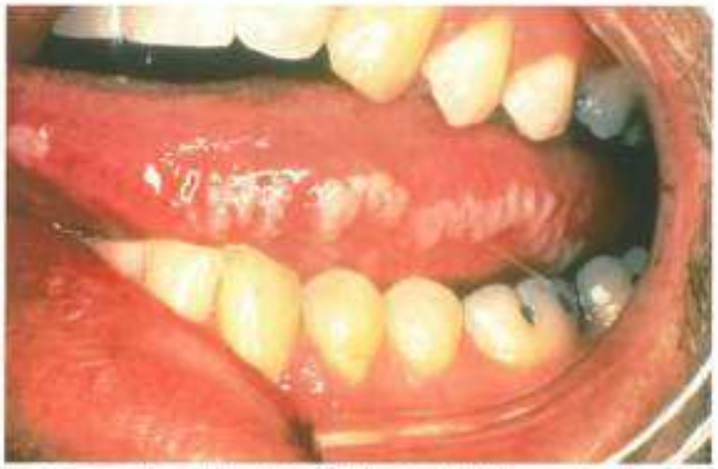


Fig. 14.76 Oral hairy leukoplakia. Prior to antiretroviral therapy this indicated a poor prognosis. There are corrugated white plaques with hairlike projections along the lateral border of the tongue. (Courtesy of Dr J. J. H. Gilkes.)

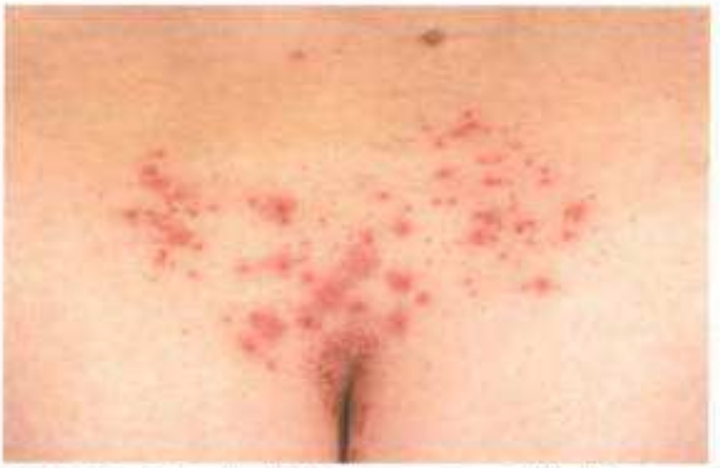


Fig. 14.77 Candidiasis. Candida infections are common in HIV-positive individuals. The perianal erythema and satellite pustules of candidiasis might suggest HIV infection in this 28-year-old male.

Fig. 14.78 Seborrhoeic eczema. The redness and scaling partly concealed by his moustache is typical of seborrhoeic eczema, probably secondary to overgrowth of *Pityrosporum* yeasts.

- **Group IV** Constitutional disease is apparent with progressive wasting, neurological disease, secondary infections and secondary malignant processes associated with full-blown AIDS. Poor prognostic signs are shrinkage of the lymph nodes, oral candidiasis and oral hairy leukoplakia. The erythrocyte sedimentation rate is raised; there is thrombocytopenia and leucopenia, with reduction of the number of $CD4^+$ cells. Antibody to p24 can no longer be detected but p24 antigen reappears in the blood. Antibodies to gp41 are still present.

The clinical manifestations of a $CD4^+$ count > 500 ($\times 10^6$ cells/L) may be asymptomatic, acute (primary) infection or generalized lymphadenopathy. 200–500 may be fever, diarrhoea, bacillary angiomatosis, candidiasis, listeriosis, herpes zoster involving more than one dermatome, cervical dysplasia or carcinoma, hairy leukoplakia, thrombocytopenic purpura and peripheral neuropathy, and < 200 AIDS-defining infections. Kaposi's sarcoma, Burkitt's lymphoma, cerebral lymphoma and HIV wasting syndrome. AIDS-defining opportunistic infections are protozoal (*Pneumocystis carinii jiroveci* pneumonia [PCP], toxoplasmosis encephalitis, cryptosporidiosis with diarrhoea), fungal (extensive and repeated candidiasis, cryptococcosis, coccidioidomycosis), viral (cytomegalovirus [including retinitis]), chronic herpes simplex [particularly chronic ulcerative lesions], progressive multifocal leucoencephalopathy) and bacteria (*Mycobacterium kansasii, Mycobacterium avium intracellulare, Mycobacterium tuberculosis*, recurrent non-typhoid salmonella bacteraemia).

Cutaneous manifestation of HIV infection

Some cutaneous conditions occur early in the disease when the $CD4^+$ cell count is still quite high, for example bacterial infections, oral hairy leukoplakia and fungal infections. Others such as xerosis and eosinophilic pustular folliculitis occur much later when the $CD4^+$ cell count is $< 200 \times 10^9$ cells/L.

- **Bacterial infections** Folliculitis, cellulitis, impetigo and abscesses.
- **Oral hairy leukoplakia** Vertically ribbed white plaques occur along the lateral borders of the tongue (Fig. 14.76) from an Epstein–Barr virus infection with or without candidal overgrowth. HAART is effective.
- **Superficial fungal infections** Dermatophytosis, pityriasis versicolor and candidiasis (Fig. 14.77) (oral, genital and intertriginous) are common. Oesophageal candidiasis causes dysphagia and retrosternal pain.
- **Seborrhoeic eczema** This may suggest the diagnosis. It is initially typical (Fig. 14.78) but may become widespread. It is thought to be caused by overgrowth or an abnormal reactivity to *Pityrosporum* yeasts.
- **Herpes simplex** Typical lesions are common but as the $CD4^+$ count falls below 100 cells per cubic millimetre, chronic and extensive non-healing infections are common, particularly around the mouth, fingers and anogenital area. Typical vesicles may be absent and erosions, deep ulceration and necrosis may be the dominant features (see Fig. 14.26). Biopsy may show cytopathic changes including multinucleated giant cells. Resistance to acyclovir and related drugs is common, usually because of reduced thymidine kinase activity and alternatives which do not require it, such as foscarnet and cidofovir, are indicated. PCR is helpful diagnostically. CMV frequently follows herpes simplex. Persistent perianal pain may occur without physical signs of herpes simplex.
- **Herpes zoster** Often affects more than one dermatome and may be disseminated and recurrent. Fatal pneumonitis may occur. Zoster frequently accompanies the immune recovery syndrome.
- **Molluscum contagiosum** This is highly characteristic, particularly on the face (see Fig. 14.49) or around the anogenital area. Giant lesions may occur.
- **Systemic fungal infections** Disseminated cryptococcosis, coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis and paracoccidioidomycosis are well-recognized complications of HIV.
- **Warts** These are more common, particularly on the face, inside the mouth and around the perineal area. High-risk HPV-16 and HPV-18 are more common and may account for the increase in cervical and anal intraepithelial neoplasia.
- **Acne** This is more common.

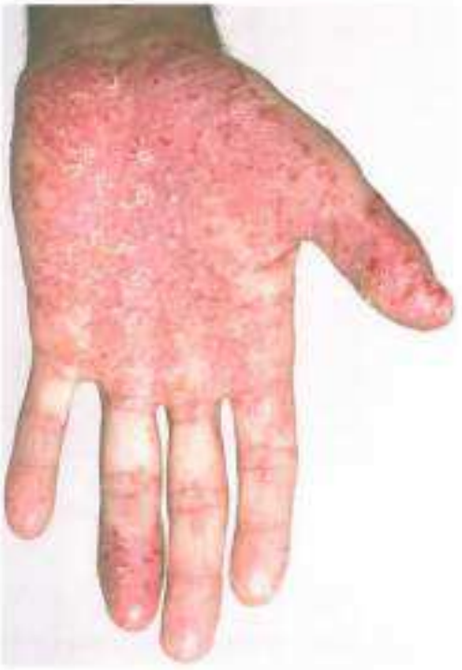


Fig. 14.79 Psoriasis. The severity and acral distribution is unusual for ordinary psoriasis. Psoriasis is five times more common in HIV-positive individuals. Note the swollen distal interphalangeal joint of the ring finger due to arthritis.

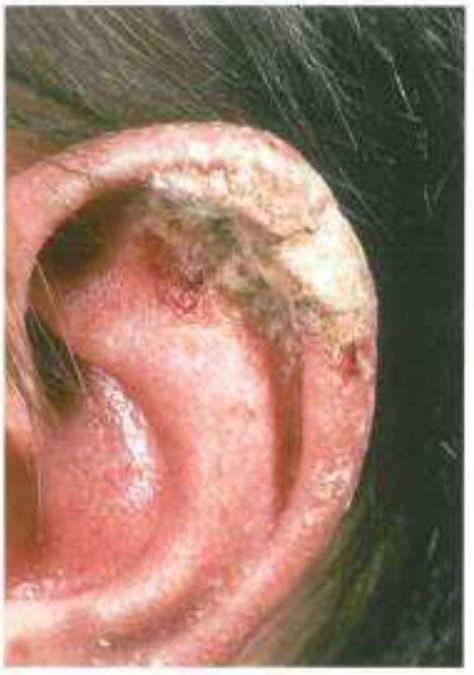


Fig. 14.80 Norwegian scabies. Crusted scabies, previously a rarity, is not unusual in HIV-positive individuals. The ears are particularly affected.

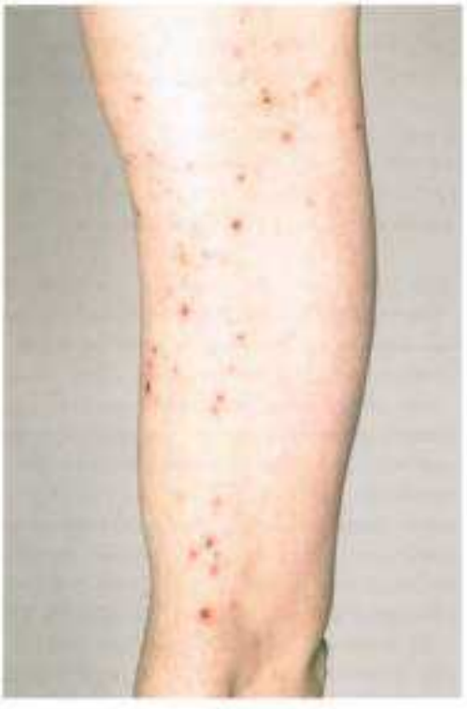


Fig. 14.81 Generalized pruritus. Generalized itching of the skin resulting in widespread excoriations is a presentation of HIV infection (papular pruritic eruption of AIDS).

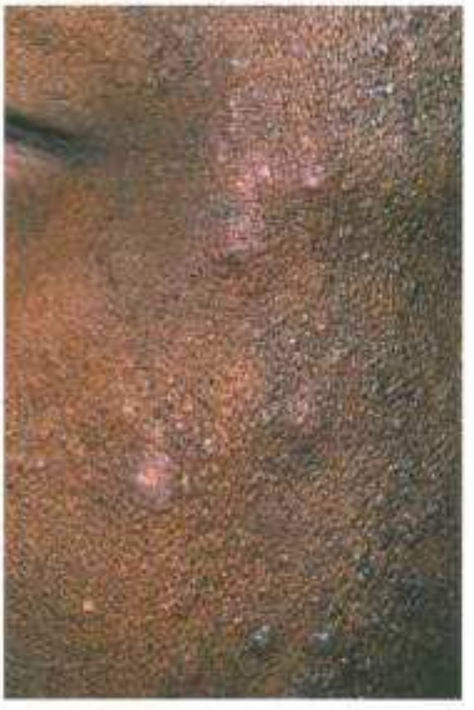


Fig. 14.82 Papulonodular demodicosis. A profuse disfiguring eruption of papules and sometimes nodules occurs on the face in immunosuppressed patients. Many demodex mites are present in biopsy material.

- **Atopic eczema** There may be a recurrence or deterioration of eczema.
- **Bacillary angiomatosis** It is caused by *Bartonella quintana* (associated with poverty and body lice) and *Bartonella henselae*, which can be cultured from blood, skin and viscera. *B. henselae* has been isolated from the blood of cats and their fleas and the condition may result from a previous cat scratch. The skin lesions are single or multiple red-purple papules or nodules of various sizes including large subcutaneous nodules that may resemble pyogenic granuloma. There may be involvement of the mouth, genitalia and internal organs (especially lungs, heart and liver) and fever, chills, night sweats, anorexia, vomiting and weight loss. Biopsy shows granulation tissue and foci of suppuration; masses of bacteria can be demonstrated with a Warthin–Starry stain. Culture of the species and PCR are helpful. Bacillary angiomatosis does respond to first- and second-generation macrolides and to tetracyclines but may require repeated courses.
- **Psoriasis** This differs from classic psoriasis in that it is more severe, responds poorly to treatment and there is a negative family history. HLA 27 is the only positive antigen in patients with asymmetrical polyarthritis. The psoriasis has particularly an acral distribution (Fig. 14.79) and is often subacute, simulating Reiter's syndrome (Ch. 5). Arthritis is common.
- **Mycobacterium avium-intracellulare infection** This is usually diagnosed by biopsy of atypical papules or nodules scattered on the limbs and trunk.
- **Norwegian scabies** Florid infestations with the acarus mite may occur, including involvement of unusual sites such as the ears (Fig. 14.80).

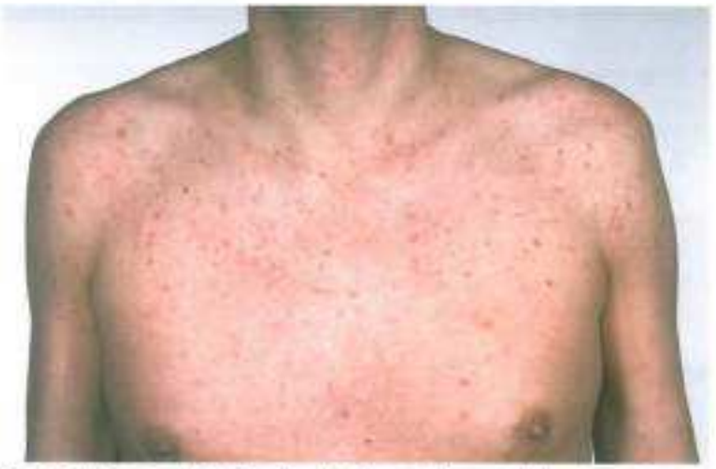


Fig. 14.83 Eosinophilic folliculitis. Multiple pruritic excoriated erythematous perifollicular papules are present. Eosinophils are found amongst the chronic inflammatory cells in the follicles on biopsy.

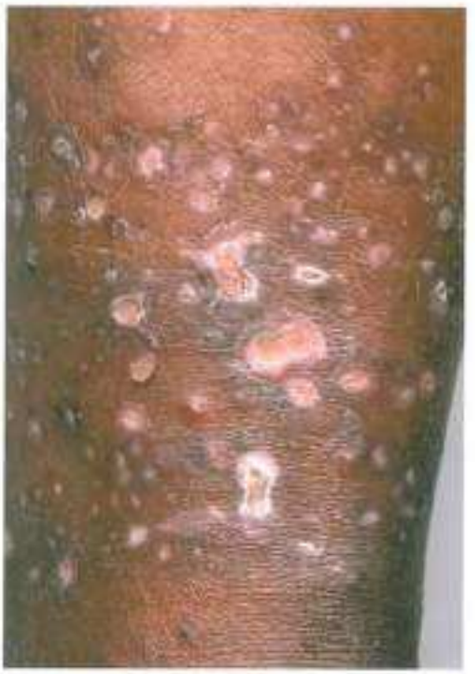


Fig. 14.84 HIV infection folliculitis. Bacterial sepsis is common. Pustules are present and crusting and considerable excoriations.

- **Generalized pruritus** This is common. There are widespread excoriations (Fig. 14.81).
- **Leishmaniasis** HIV patients are more susceptible to this protozoan infection and there may be recrudescence of a previous latent infection.
- **Syphilis** All patients should be tested and for other sexually transmitted infections. The clinical features are usually typical, but lues maligna (Ch. 13) is more common.
- **Papulo-nodular demodicosis** Rosacea-like papules occur on the face (Fig. 14.82). Skin scrapings or biopsy shows numerous demodex mites. Topical permethrin or oral metronidazole or ivermectin are effective.
- **Eosinophilic pustular folliculitis** HIV-associated eosinophilic folliculitis is seen mainly in Caucasian homosexuals. It appears late with low $CD4^+$ counts or as part of the immune reconstitution syndrome. A similar condition occurs after organ transplantation. It causes chronic intractable pruritus. There are erythematous perifollicular papules, with occasional pustules that are heavily excoriated, mainly on the trunk but also on the head and neck (Fig. 14.83). There may be a peripheral eosinophilia in 25–50%. IgE is significantly raised but microbiology is negative. There is a diagnostic histology of chronically inflamed follicles with lymphocytes and eosinophils especially around the follicular isthmus and sebaceous glands and ducts. There is striking sebaceous lysis and a perivascular inflammation. It should be distinguished from *HIV-associated infective folliculitis* (Fig. 14.84) and from *Ofuji's disease*, which has the same histology but is a different disease affecting healthy patients and with pruritus occurring in only 50%. The cause of eosinophilic folliculitis is not known but is possibly secondary to *Pityrosporum* infection. It has been treated with permethrin, itraconazole, metronidazole, isotretinoin and ultraviolet B or psoralen with ultraviolet light (PUVA). The last is quite effective but since the advent of HAART, the incidence of eosinophilic folliculitis has decreased.
- **Kaposi's sarcoma** This multifocal endothelial cell neoplasm (Fig. 14.85) is caused by HHV-8. It is becoming much less common with the use of HAART, but is a serious illness still in sub-Saharan Africa (see Ch. 10).
- **Xerosis** This is common in the later stages particularly with wasting or as an acquired ichthyosis with malignancy.
- **Drug eruptions** Drug hypersensitivity, particularly to sulphonamides (Fig. 14.86) and other antibiotics, is common.

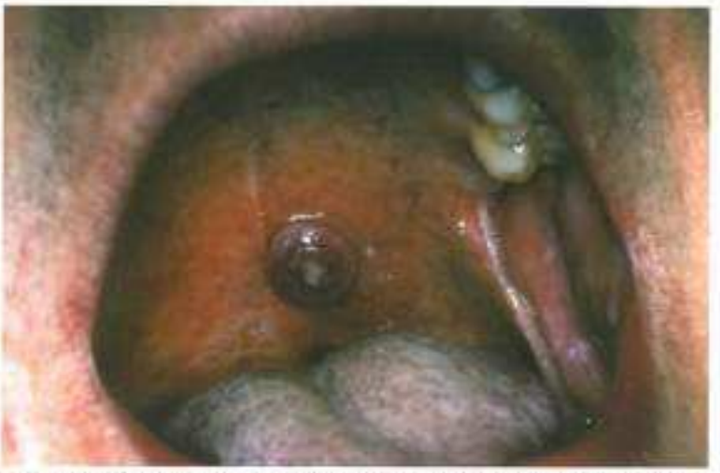


Fig. 14.85 Kaposi's sarcoma. Purple plaques and nodules occur anywhere on the skin including in the mouth.

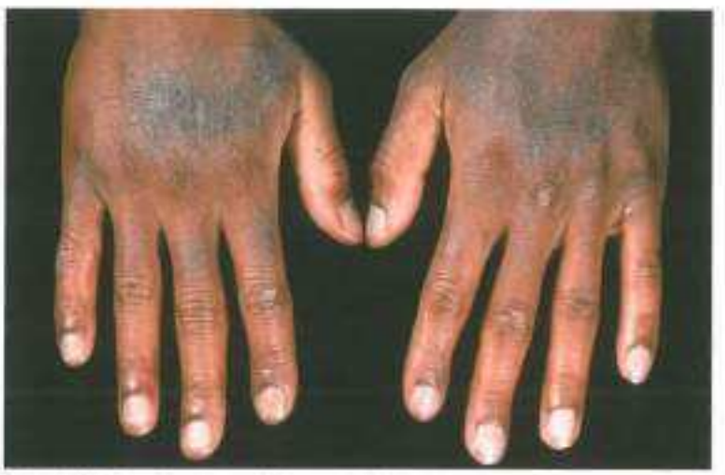


Fig. 14.86 Drug hypersensitivity and HIV infection. Drug-induced eruptions are very common. This man has a photosensitivity to co-trimoxazole, which is affecting the backs of the hands and his face.

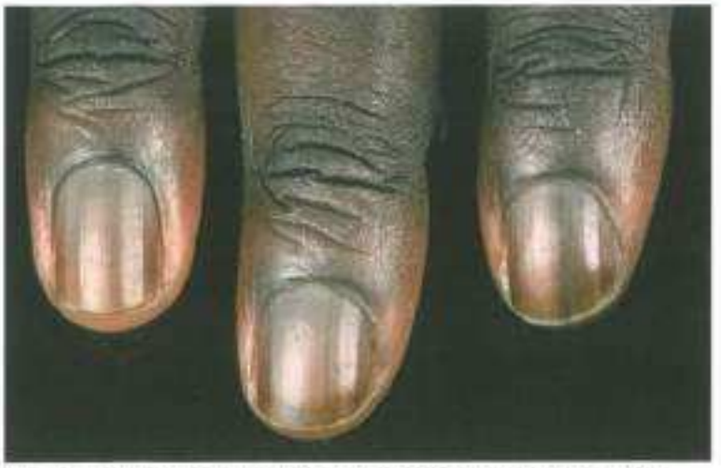


Fig. 14.87 Nail pigmentation. Diffuse pigmentation of the nails is frequently observed in those taking zidovudine.

- **Lymphoma of the skin** Aggressive B cell lymphomas with extranodal presentations are common. Cutaneous T cell lymphomas are rare but erythrodermas and mycosis fungoides-like lesions do occur.
- **Diffuse granuloma annulare** This has been reported.
- **Nail disorders** These include:
  - proximal white subungual onychomycosis caused by *Trichophyton rubrum* rather than the more usual *Trichophyton mentagrophytes*; both hands and all fingernails are affected especially if the $CD4^+$ T cells are $< 100 \times 10^6$ cells/L
  - candidiasis, including a hypertrophic nailbed variety that is similar clinically to that of chronic mucocutaneous candidiasis
  - acute paronychia with staphylococci or pseudomonas are not unusual
  - herpes simplex whitlows
  - periungual warts, which have occasionally proceeded to squamous cell carcinoma
  - melanin pigmentation of the nails may occur with zidovudine (Fig. 14.87).
- **Photosensitivity** Porphyria cutanea tarda, chronic actinic dermatitis and photolichenoid drug eruptions are more common in HIV infections.
- **Persistent acrocyanosis** In some HIV-positive individuals, other activities may lead to cutaneous conditions. For example, prolonged stasis and sludging may occur secondary to peripheral vasodilatation caused by the abuse of smooth muscle relaxants (butyl nitrite) as aphrodisiacs.
- **Immune reconstitution syndrome** This may follow institution of HAART, particularly in those with the greatest immunosuppression and the highest burden of antigen from dead or alive organisms. It results in a paradoxical deterioration in certain fungal, herpetic, *mycobacterium avium intracellulare* and other opportunistic infections and inflammatory disorders.
- **Drug eruptions** All forms are increased. Nevirapine particularly causes toxic epidermal necrolysis (TEN). Risk factors include low body weight and an AIDS-defining illness. HAART is responsible for the lipodystrophy syndrome (lactic acidosis, dyslipidaemia, dysregulation of glucose metabolism, osteopenia and lipoatrophy). Lipoatrophy is manifest by loss of subcutaneous tissue in the face, limbs and buttocks. It may be treated with fillers. Fat may accumulate in the front of the neck, upper trunk, breasts, dorsocervically and in the abdomen. Lipomas are more common.

Management

The treatment of HIV infections has been revolutionized by the combination of one or more nucleoside reverse transcriptase inhibitors with a protease inhibitor. This highly active anti-retroviral therapy (HAART) reduces the viral titres to virtually undetectable levels and significantly prolongs the period when $CD4^+$ cell numbers are elevated. Zidovudine (formerly called azidothymidine; AZT) lamivudine, stavudine and zalcitabine and didanosine are examples of nucleoside reverse transcriptase inhibitors. Ritonavir, saquinavir, indinavir are examples of protease inhibitors. The latter do inhibit P-450 enzyme systems and may interact with other drugs that do the same. These drugs are given during primary HIV infection, established HIV infection and where there may be perinatal transmission or following a needlestick injury. HAART reverses T cell depletion sequentially starting with the memory T cells until there is complete reconstitution of the T cell receptor repertoire. There is a dramatic decrease in infections with *Pneumocystis carinii*, *Mycobacterium avium-intracellulare* complex and cytomegalovirus (retinitis). Paradoxically, herpes zoster may reappear as the $CD4^+$ cell count rises, but this treatment has made an enormous difference to the management of Kaposi's sarcoma, molluscum contagiosum, eosinophilic folliculitis, verrucous herpes zoster, refractory bacterial folliculitis, warts and Norwegian scabies. Persistent drug eruptions also clear as the viral load (the concentration of HIV RNA in the plasma) decreases and the $CD4^+$ cell count rises.

Specific infections should be treated with the appropriate agents. Of particular note, chronic perianal herpes infections have been treated with foscarnet, which unlike aciclovir does not need to be phosphorylated to be effective. Many herpes simplex isolates are thymidine kinase deficient in HIV infections and are, therefore, resistant to aciclovir therapy. Cidofovir is a nucleotide analogue that is approved for the treatment of cytomegalovirus retinitis in AIDS. It also has widespread spectrum against DNA viruses because it inhibits viral DNA polymerase; it is reported as being effective in molluscum contagiosum and a topical formulation is under evaluation. Imiquimod is an interferon immune enhancer. It can be used topically and has all the benefits of interferon without its limitations and has been used to treat persistent warts in HIV disease. Foscarnet and aciclovir have been used to treat oral hairy leukoplakia, but famciclovir has a long intracellular half-life and high oral bioavailability and may be preferable.

Superficial fungal disorders of the skin

15

Fungi have a true nucleus with a nuclear membrane and are known as eukaryotes. They may be uni- or multicellular. Their cell walls contain chitin and cell membranes ergosterol. Antifungal agents work either by interfering with ergosterol synthesis or by interfering with nuclear activity.

Fungi require an organic source of nitrogen and carbon, such as carbohydrate, for culture. There are various media available: Sabouraud's glucose agar is the standard; Mycosel is more selective for dermatophytes. However, the latter contains chloramphenicol and cycloheximide which inhibit contaminants, but also important pathogens such as *Scopulariopsis brevis* and *Aspergillus* species. Fungi have two distinct forms on culture – yeasts and moulds. Some exhibit both. Yeasts are slimy or mucoid. Moulds are downy, fluffy or granular. In the commensal state, yeast cells are ovoid, but in the pathogenic state they bud to produce pseudohyphae. Hyphae and conidia are found in the mould phase.

Candidiasis, pityriasis versicolor and the dermatophyte infections are traditionally known as superficial infections in that they do not penetrate beyond the superficial layers of the skin, except sometimes in the immunocompromised. Subcutaneous implantation and deep fungal infections, such as blastomycosis or coccidioidomycosis, are covered in Chapter 17.

Candidiasis

Candidiasis is a common infection of the mouth, genitalia, flexures and nails (see Ch. 25), usually caused by *Candida albicans*, an oval yeast, which in its pathogenic state divides by budding, producing pseudohyphae (Fig. 15.1). On culture it has a pasty appearance (Fig. 15.2).

The yeast is harboured as a commensal in the oropharynx, gastrointestinal tract or vagina in 80% of normal individuals. It is rarely found on normal skin, except in areas of increased moisture and temperature such as occluded intertriginous sites. *Candida* thrives when the stratum corneum is damaged, for example where two apposing folds of skin rub together in the flexures, in the obese, or under an ill-fitting denture.

Candidiasis is more common at the extremes of age, during pregnancy or the menses and in diabetes mellitus, Cushing's disease, uraemia and malignant disease. Immunodeficiency – humoral and, more especially, cell mediated (which is the major fault in the rare disease *chronic mucocutaneous candidiasis*) – is a frequent cause. Oral pharyngeal candidiasis is an acquired immunodeficiency syndrome (AIDS)-defining illness. Neutropenic patients are particularly vulnerable because phagocytosis of the yeast depends on functioning polymorphonuclear leucocytes and macrophages. Rare species such as *Candida krusei* may be found in the skin in these patients. Neonates may contract it from the birth canal. A widespread erythroderma with papules and pustules followed by desquamation results.

Candida is an opportunist and benefits from iatrogenic opportunities. Broad-spectrum antibiotics eradicate the microbial flora that compete with *Candida* species for nutrients, thus allowing the yeast to flourish. Systemic and topical steroids are immunosuppressive and favour overgrowth with *Candida* species. Indwelling urinary and vascular catheters and intravenous drug abuse provide opportunities for systemic candidiasis.

Chronic mucocutaneous candidiasis presents in childhood or adolescence. Familial cases usually affect the mouth and there is parental consanguinity. *Candida* granulomas may be present on the scalp, face and mouth. There is an autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED). It is an autorecessive disorder with mutations in AIRE, which encodes a DNA transcription factor. It particularly affects Sardinians, Iranian Jews and the Finns. *Candida* infections present first and then the endocrinopathy (hypopituitarism, hypothyroidism, hypoparathyroidism, hypoadrenocorticism, hypogonadism and type 1 diabetes mellitus). There may be general autoimmune disorders including pernicious anaemia, chronic active hepatitis, vitiligo and alopecia areata.

Chronic mucocutaneous candidiasis may result from an immunodeficiency (severe combined, DiGeorge or hyper IgE) syndrome or a non-immunological disorder, such as KID, acrodermatitis enteropathica, multiple carboxylase deficiency or ectodermal-ectrodactyly-clefting syndrome.

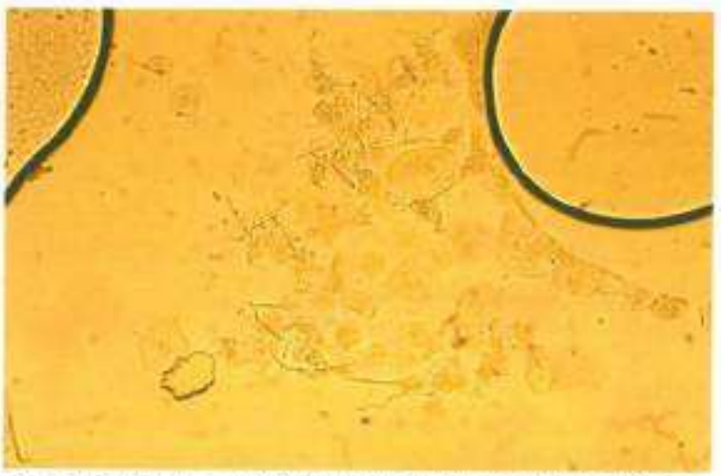


Fig. 15.1 *Candida albicans*. Oval yeasts are present. They divide by budding and produce pseudohyphae. (30% potassium hydroxide preparation (x128). Courtesy of Miss G. Midgley.)

Fig. 15.2 *Candida albicans*. This organism is a yeast. It has a pasty appearance on culture. (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

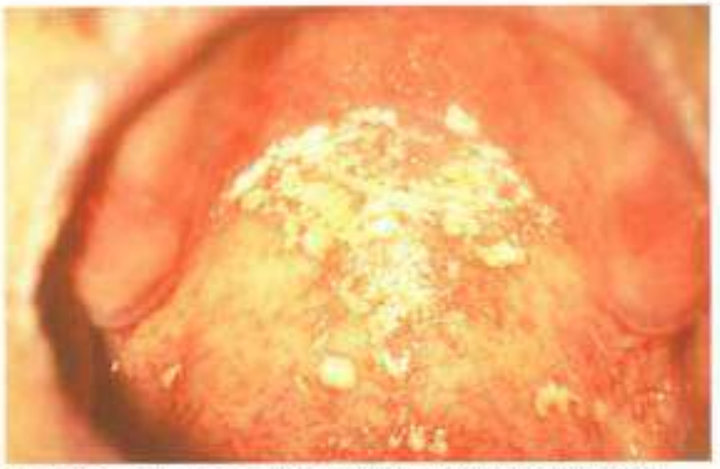


Fig. 15.3 *Candida albicans*. White and yellow pustules are present on the palate. Immunodeficiency, diabetes and poor dental hygiene are common causes.

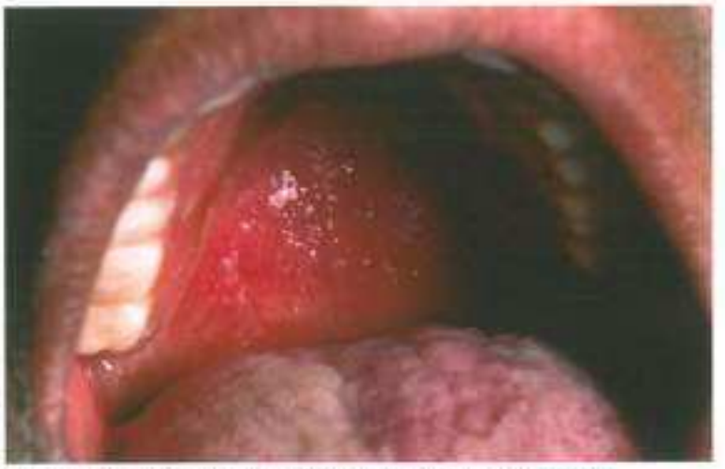


Fig. 15.4 *Candida albicans*. The palate has a red raw slightly eroded appearance once the pustules have broken. Note the false teeth. Dental plates favour opportunistic infection.

ORAL CANDIDIASIS (THRUSH)

An infection of the mouth by the yeast *C. albicans*.

Aetiology

Common in the neonatal period, when immunological defence systems are poorly developed, it is contracted from the mother during vaginal delivery. The very sick and immunosuppressed are at risk. Healthy edentulous individuals who neglect their oral and denture hygiene may be affected.

Clinical Features

Symptoms

The infant may be in distress or present with feeding difficulties, whereas the adult with oral candidiasis complains of a sore mouth.

Morphology

There are well-defined white or cream-coloured pustules (Fig. 15.3).

Distribution

The palate, tongue, buccal mucous membranes or gums. The pustules may be scraped with a spatula, leaving a red, raw, bleeding base (Fig. 15.4).

Differential Diagnosis

Rarely misdiagnosed, although lichen planus (see Fig. 7.55) is sometimes mistaken for it. The organism may be grown on culture of a swab from a pustule.

ANGULAR CHEILITIS

A red, raw, scaly condition at the angles of the mouth, caused by *C. albicans*.

Aetiology

Although classically described in the malnourished or immunosuppressed (including HIV), angular cheilitis is common in those who are either edentulous or who wear dentures that do not fit properly. The configuration of the mouth becomes distorted and sags; as a result, the upper lip tends to overhang the lower and a groove forms at the corners of the mouth. Saliva trickles imperceptibly down the fold, which becomes moist and provides a perfect habitat for *C. albicans*. The patient often sleeps with the denture in position and cleans it infrequently, or not at all, which traumatizes the gums and palate, so facilitating the entry of organisms including *Staphylococcus aureus*. Sometimes both organisms coexist.

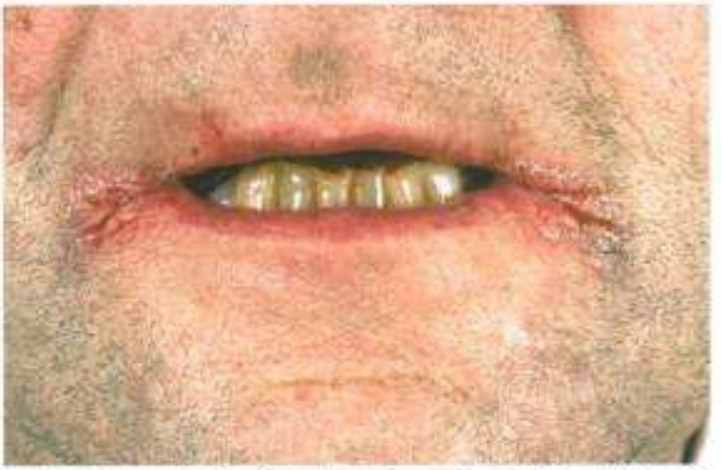


Fig. 15.5 Angular cheilitis. Red and raw fissures occur, particularly in those with ill-fitting dentures, which distort the contours of the mouth.

Clinical Features

Symptoms

There is a sore rash at the angles of the mouth (Fig. 15.5).

Morphology

The skin is raw and fissured with adjacent erythema and slight scaling.

Distribution

There is associated downturning of the corners of the mouth.

Genital candidiasis

CANDIDA VULVOVAGINITIS

A vaginitis which may spread to the vulva, caused by *C. albicans*.

Aetiology

It is common in young, otherwise healthy women, often precipitated by broad-spectrum antibiotics, oral contraceptive therapy (particularly if prescribed together), copper-containing intrauterine devices or pregnancy. *C. albicans* is a commensal in the skin, mouth, alimentary tract and vagina; although sexual transmission occurs, the gastrointestinal tract may well

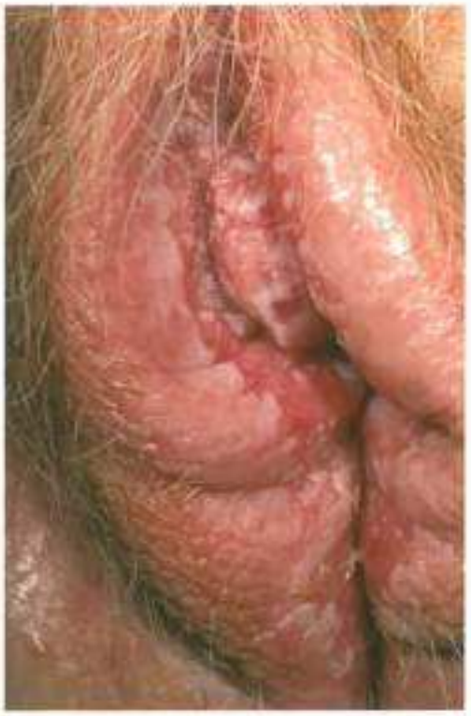


Fig. 15.6 Candida vulvovaginitis. A white discharge occurs with white pustules. If neglected, the pustules are followed by erosions and oedema occur on the vulva.

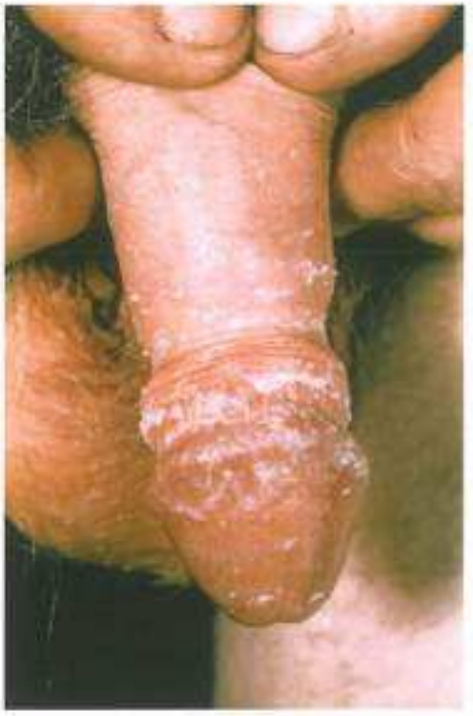


Fig. 15.7 Candida balanitis. The glans is studded with yellow pustules. It is more common in the uncircumcised. (Courtesy of Dr F. Lim.)

be a more important source of the infection. In addition, tight-fitting clothing (for example jeans) produces an occluded warm and moist environment that compounds the problem. Candida vulvovaginitis can be a presentation of diabetes mellitus in middle-aged, often overweight females.

Clinical Features

Symptoms

The vulva and vagina are itchy and sore and there is a discharge.

Morphology and distribution

A thick, abundant cream-coloured discharge occurs, with pustules that become eroded and raw on the vulva with oedema (Fig. 15.6).

CANDIDA BALANITIS

An infection of the glans penis with *C. albicans*.

Aetiology

It is usually acquired from a sexual partner who has active disease. It is much more common in the uncircumcised as the prepuce provides an ideal occluded, moist, warm environment in which the yeast may flourish.

Clinical Features

Symptoms

There are tiny pustules on the penis, which rupture quickly.

Morphology

The glans may be red and swollen with yellow pustules (Fig. 15.7).

CANDIDA INTERTRIGO

An infection with *C. albicans* between two apposing skin surfaces.

Aetiology

Intertrigo is a term used to refer to an eruption between two apposing skin surfaces. Other skin disorders which occur in intertriginous areas are seborrhoeic eczema, psoriasis, erythrasma and tinea. The axillae, groins, submammary regions and folds secondary to obesity are the most common sites. The nailfolds (Fig. 15.8) and the skin between the fingers are also potentially intertriginous sites, particularly in those who frequently have wet hands. They are ideal sites for candidiasis since they are warm, moist and subject to friction.

Clinical Features

Symptoms

Candida intertrigo appears as a pustular rash in the flexures.

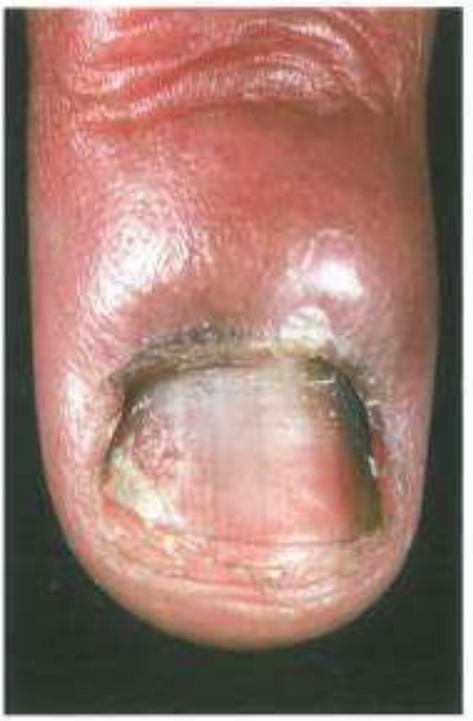


Fig. 15.8 Candida paronychia. Candida is an opportunist and invades because the seal to the posterior and lateral nailfolds (the cuticle) is damaged, particularly by excess immersion in water. The nailfold becomes swollen and when the nail is affected, it is discoloured.

Morphology

Initially there are pustules surrounded by erythema, which then become confluent and break, leaving red, raw eroded skin (Fig. 15.9). The outer margins of the eruption are often macerated, and the skin appears white, thickened and sodden. Satellite pustules are characteristic arising away from the central core of the rash (Fig. 15.10).

Distribution

Particularly in the groin, axillae and perianal and submammary regions. When it occurs between the finger webs (Fig. 15.11) it is known as *erosio interdigitale*.

Management of Candidiasis

A swab should be taken for microscopy and for culture to confirm the diagnosis. The urine should be tested for glucose, and a full blood count requested to rule out immunodeficiency.

Oral candidiasis can usually be remedied with nystatin oral suspension, amphotericin (lozenges or oral suspension) or miconazole nitrate oral gel. Oral hygiene is of the utmost importance in the prevention of candidiasis in sick patients who cannot clean the mouth and teeth properly.

Patients with angular cheilitis should not sleep with the dentures in the mouth and should be taught to sterilize the dentures overnight. Faulty dentures should be corrected by the dentist. Antimicrobial agents alone are often not effective for cheilitis because the inflammation will not respond. This is one of the few occasions for polypharmacy, that is, a combination product containing an anti-inflammatory (1% hydrocortisone), an antifungal and, often, an antibacterial agent. Suitable combinations are nystatin, hydrocortisone and benzalkonium; nystatin, hydrocortisone and chlorhexidine; clioquinol and hydrocortisone; miconazole and hydrocortisone. In severe cases, a facelift is sometimes necessary to correct the groove at the angles of the mouth.

Genital candidiasis may be treated with nystatin or imidazole creams and, in female patients, pessaries. Oral imidazoles are sometimes required. Precipitating causes – antibiotics, oral contraceptives, partner infection and diabetes – should be remedied.

Intertrigo responds to anticandidal creams or ointments. Combination with hydrocortisone, and sometimes an antibacterial agent, is often necessary. Old-fashioned preparation, such as Castellani's paint (0.4% magenta, 4% phenol with resorcinol, acetone, industrial methylated spirits and water) or 0.5% aqueous gentian violet, are very helpful in severe intertrigo. Oral imidazoles may be necessary.

Drugs used in management of candidiasis include:

- **Nystatin** This is a polyene antibiotic which is effective topically. Its disadvantage is that it is yellow and can stain clothing. It can be taken orally, because it is not absorbed, and is used to sterilize the gut in recurrent infections.
- **Amphotericin** This is another polyene antibiotic. It is used in a similar manner to nystatin. Both are ineffective against other superficial fungi but amphotericin is used systemically for deep mycotic infections.
- **Imidazoles** These are easy to use topically. They have a broad spectrum, being also effective against tinea and pityriasis versicolor.
- **Fluconazole** This is a broad-spectrum triazole that is effective against dermatophytes, most *Candida* species, some non-dermatophyte moulds and cryptococcal meningitis. It has a low molecular weight with high water solubility, resulting in good bioavailability. It does not need to be taken with food and accumulates and persists for a significant period in the stratum corneum and nails. It inhibits fungal cytochrome P-450 enzymes and, therefore, may interact with other drugs that do the same. It is given as a single day dose of 150 mg orally to treat genital candidiasis. In other conditions, it may be given in a dose of 100–400 mg daily for a week. It is given prophylactically for the long-term management

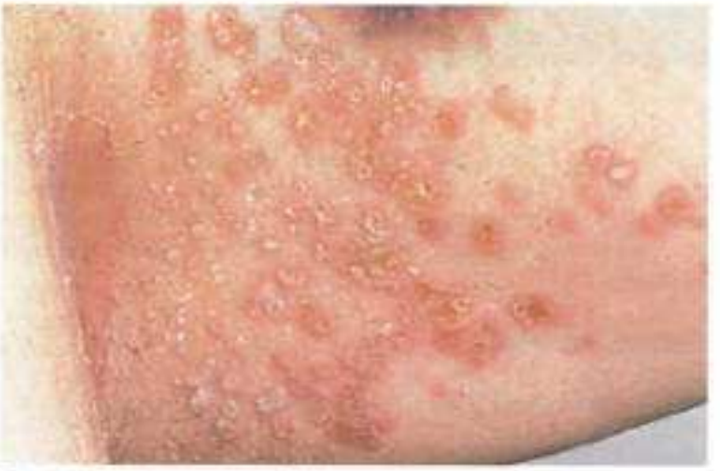


Fig. 15.9 Candida intertrigo. Satellite pustules are radiating out from a raw area in the axilla. The eruption occurred in this humid intertriginous area because she had broken her arm (note bruising) and it was painful to move it.

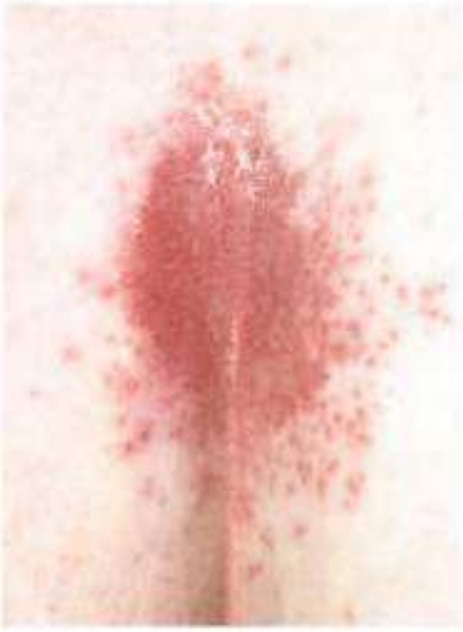


Fig. 15.10 Candida intertrigo. A raw erythema is present in the natal cleft, with satellite pustules away from the central eruption. This lady was found to have glycosuria.

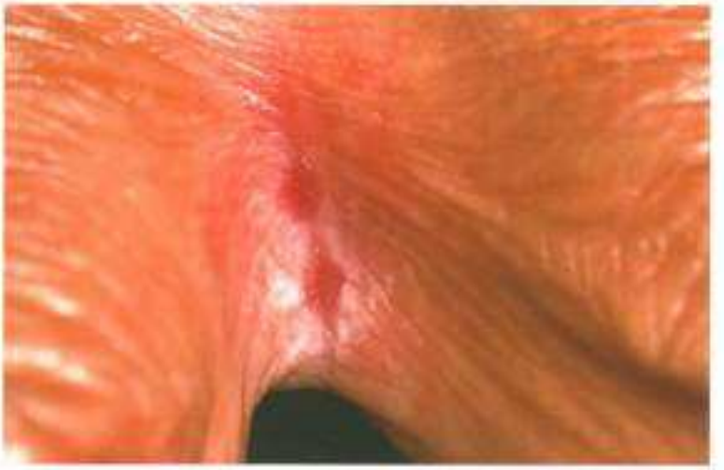


Fig. 15.11 Erosio interdigitale. There is a central erosion surrounded by maceration. This candida infection occurred in a gynaecologist who washed her hands after each consultation but failed to dry them carefully.

of oropharyngeal candidiasis in those with AIDS and also long term for patients with chronic mucocutaneous candidiasis. Unfortunately, resistance to fluconazole is being reported in these patients.

- **Itraconazole** This is a triazole that interferes with the conversion of lanosterol to ergosterol in the cell wall of the fungus. Membrane leakage occurs, the organism stops reproduction and there is gradual cell death. It is fungistatic. Itraconazole is lipophilic and has a high affinity for keratinizing tissue. It may persist for up to 6 months and, therefore, remains in the nails after discontinuation of therapy. It is metabolized by the P-450 enzyme system and, consequently, may interact with other drugs. It is a teratogen in some animal species and should be avoided in women who might become pregnant; it is excreted in human milk. It has to be taken with meals because its absorption characteristics vary. The single day oral dose for genital candidiasis is 600 mg but the usual daily dose for other conditions is 100–200 mg daily for 7 days or more.

Pityriasis versicolor

An infection mainly of the torso caused by a yeast that is ordinarily a commensal but becomes pathogenic in warm, humid conditions.

Aetiology

It is caused by the unicellular yeasts *Pityrosporum orbiculare* and *Pityrosporum ovale*. They are commensals of the skin, but also opportunists and become pathogenic by budding and producing filaments known as pseudohyphae (when the organism is sometimes known as *Malassezia furfur*). The yeast is lipophilic, so the condition is rarely seen in the West before puberty and maturation of the sebaceous gland. It is a common disorder of young adults.

Growth in the stratum corneum (Fig. 15.12) is encouraged by an increase in environmental temperature and the use of suntan oils; therefore, many patients notice that the condition begins after a summer vacation. It is a disorder of the healthy, but the immunosuppressed are at risk. It is common in lymphoma, Cushing's disease or syndrome, diabetes mellitus, AIDS, malnutrition and patients on immunosuppressive therapy. Topical glucocorticosteroids account for many of the widespread cases. The fungus is of low infectivity and it is unusual for the disorder to be transmitted to another person.

The yeast is found in large amounts in dandruff and seborrhoeic dermatitis probably as a secondary opportunist and may explain why these conditions are more common in association with HIV. An itchy folliculitis seen in young adults primarily on the trunk does appear to be caused by *P. orbiculare* (*pityrosporum folliculitis*, see below).

Clinical Features

Symptoms

Asymptomatic patches that are either brown or do not tan properly. Patients recognize that there is something wrong with pigmentation.

Morphology

The condition starts as a macule, sometimes surrounding the orifice of a hair follicle, which grows insidiously and coalesces with other macules, producing various shapes and sizes (Fig. 15.13) in an asymmetrical distribution. Since the fungus invades the stratum corneum, the condition is scaly; this may not be immediately obvious, but it can be highlighted by scraping the surface with a blunt scalpel. Many fine scales (pityriasis) can then be seen on the blade. This sign disappears after treatment.

The colour of the lesions varies. In dark skin, the macules may be darker or lighter than the surrounding normal skin and may vary in any one individual (Fig. 15.14). In an untanned Caucasian, the lesions are brown or

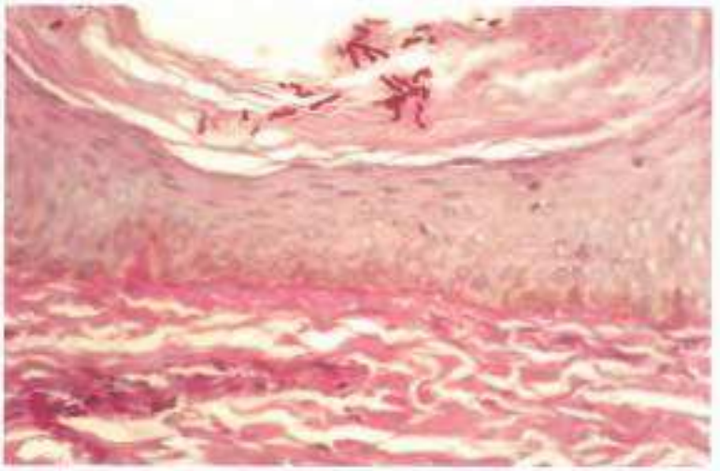


Fig. 15.12 Pityriasis versicolor. The fungus, like other superficial fungi, lives in the stratum corneum. The pseudohyphae are visible here stained purple with periodic acid–Schiff (PAS).

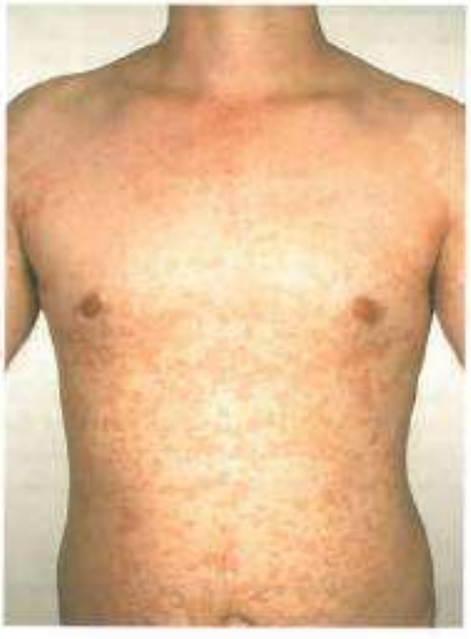


Fig. 15.13 Pityriasis versicolor. Fawn-coloured macules are characteristic and may become extensive if mistreated with topical steroids.

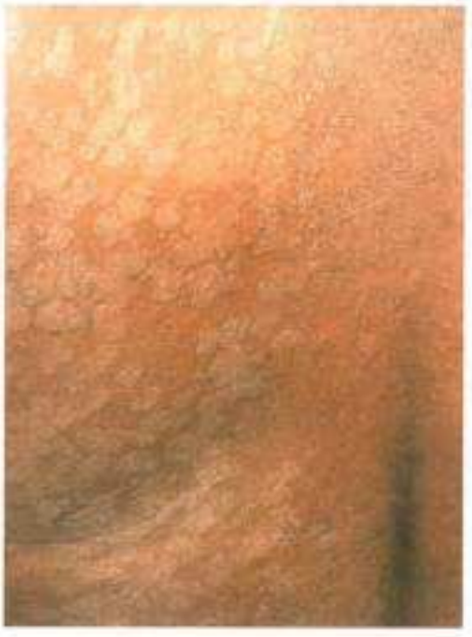


Fig. 15.14 Pityriasis versicolor. Hypo- and hyperpigmented macules (hence versicolor) occur. The fine scaling is very clear in this West Indian.

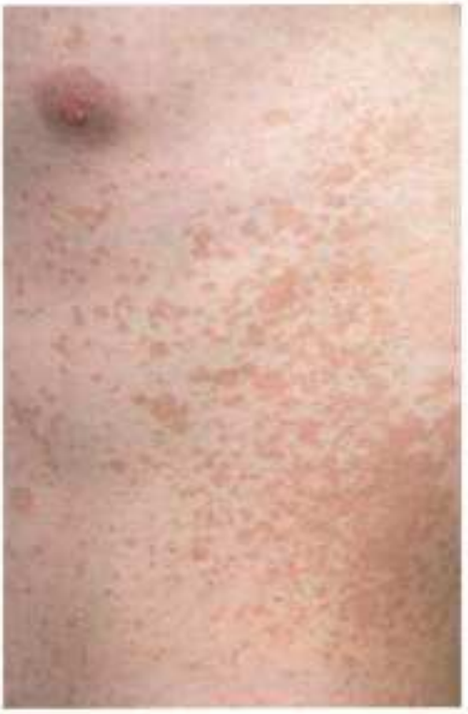


Fig 15.15 Pityriasis versicolor. Fawn-coloured macules are characteristic and may become extensive if mistreated with topical steroids.

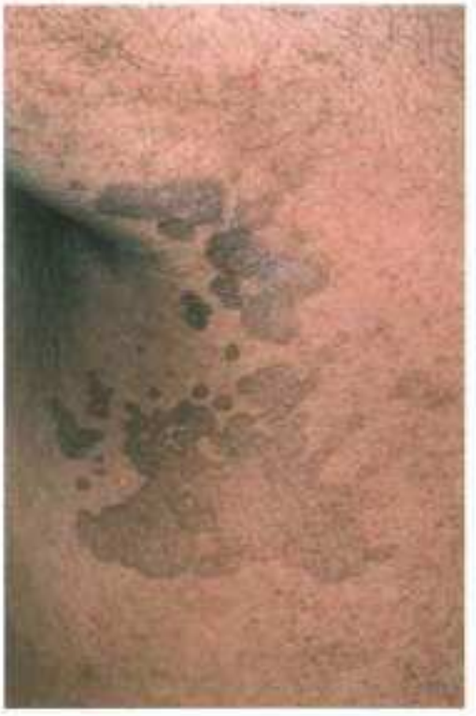


Fig. 15.16 Pityriasis versicolor. The macules may merge into each other becoming confluent brown patches with various shapes and sizes. Scraping the skin with a blunt scalpel will reveal fine scales and the yeast can be demonstrated microscopically at the bedside.

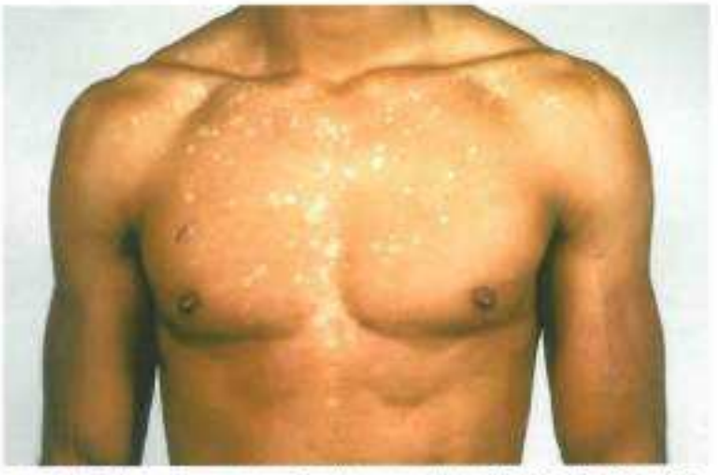


Fig. 15.17 Pityriasis versicolor. The fungus produces dicarboxylic acids which temporarily impair melanocytic function, resulting in hypopigmented macules.

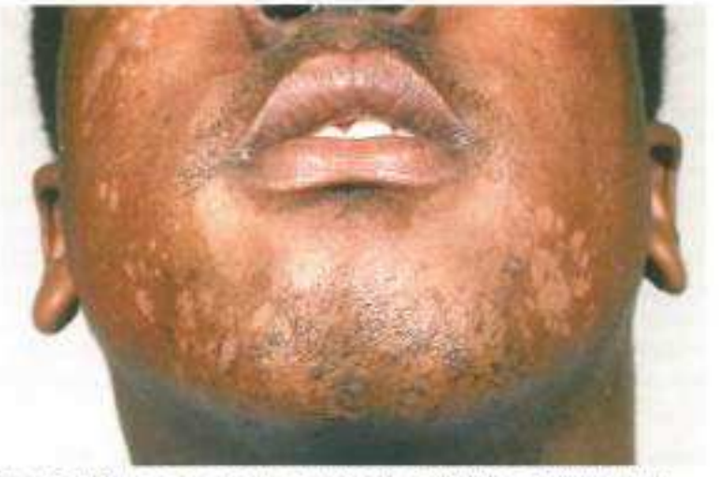


Fig. 15.18 Pityriasis versicolor. It rarely occurs on the face. However, in this patient, scrapings from these hypopigmented macules revealed oval yeasts and pseudohyphae on direct microscopy with potassium hydroxide.

fawn coloured (Figs 15.15 and 15.16); however, if a suntan is acquired, the lesions appear pale in comparison with the surrounding tanned skin. This is partly because the melanocytes are shielded from ultraviolet radiation by the diseased skin, but there is also evidence that the melanocytes are temporarily damaged by dicarboxylic acids produced by the fungus. Repigmentation may take many months. Indeed, in individuals who are suntanned, these off-white patches are often misdiagnosed as incurable vitiligo (Fig. 15.17). Vitiligo, however, is usually symmetrical, more widespread and is completely white.

Distribution

The front of the chest, neck and back. The limbs are rarely affected, except in extensive infections where topical steroids have been erroneously prescribed. It is unusual for the face to be involved (Fig. 15.18), despite the high density of sebaceous glands and therefore the lipid substrate favoured by the organism. The occlusive effect of clothing may explain this difference in distribution.

Differential Diagnosis

A condition known as *confluent and reticulate papillomatosis* (Gougerot–Carteaud syndrome), characterized by red-brown macules that become confluent and have a reticulate or net-shaped appearance, particularly in the axillae (Figs 15.19 and 15.20) and other flexures but also over the breasts and back, may simulate pityriasis versicolor. However, microscopy is negative and it does not respond to antifungals but does to minocycline.

Management

Pityrosporum species are easy to demonstrate microscopically. The lesion is scraped with a blunt scalpel, and the scales are put onto a microscope slide.

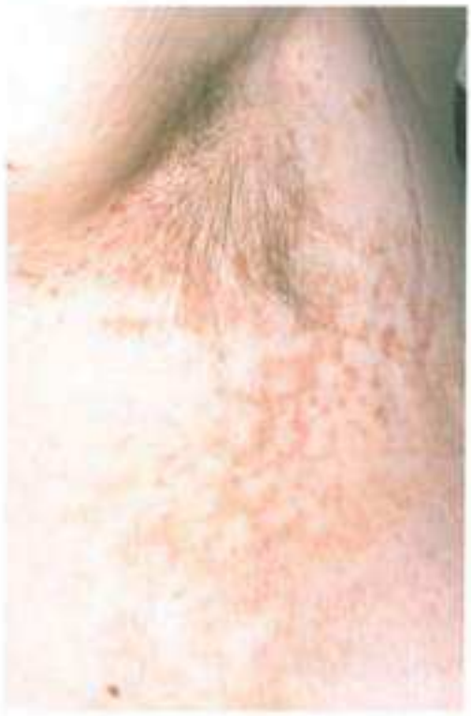


Fig. 15.19 Confluent and reticulate papillomatosis. There are brown scaly macules arranged in a net-like pattern. Scrapings are negative for *Pityrosporum orbiculare* and it does not respond to antifungals, but does to antibiotics such as minocycline.

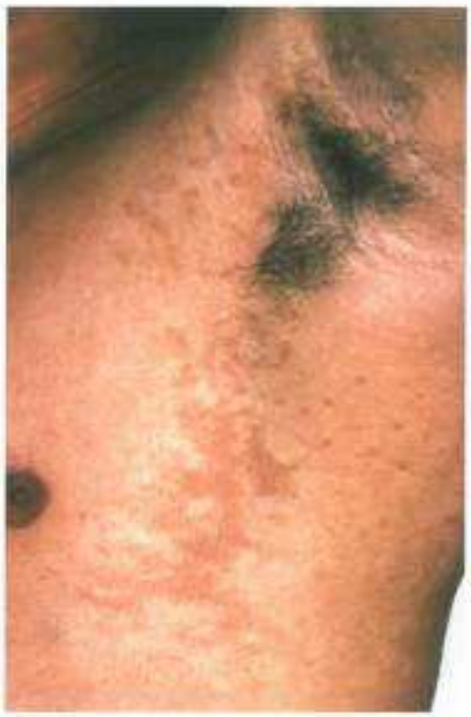


Fig. 15.20 Confluent and reticulate papillomatosis. The condition occurs in white and black skins. It is the net-like appearance that is so characteristic of the condition.

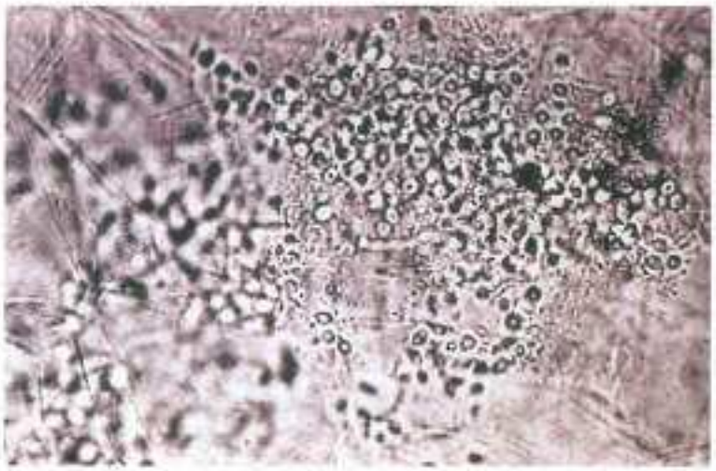


Fig. 15.21 Pityriasis versicolor. In the presence of potash (potassium hydroxide) thick-walled spherical yeasts with pseudohyphae can be seen, sometimes referred to as a 'spaghetti and meatball' appearance.

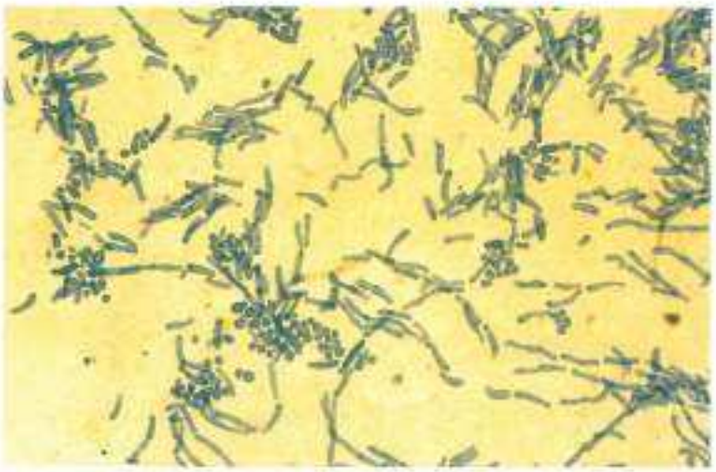


Fig. 15.22 Pityriasis versicolor. Potassium hydroxide (30%) in equal parts with Parker's blue-black ink stains the pseudohyphae and spherical yeasts in skin scrapings (*Malassezia furfur*).

In the presence of 30% potassium hydroxide (potash), thick-walled, spherical yeasts with pseudohyphae can be visualized (Fig. 15.21). Since the yeast takes up certain ink stains, the best preparations are made by adding equal parts of Parker's blue-black ink to the potassium hydroxide so that the blue ink highlights the organism (Fig. 15.22) or with 1% Chicago sky blue 6B and 8% KOH. The diagnosis can also be established by examining the skin under a Wood's light: the affected areas fluoresce a yellow colour.

There are a number of commonly used treatments.

- **Half-strength Whitfield's ointment** This is 3% salicyclic acid, 6% benzoic acid and 64% cocois oil in soft paraffin. Irritation is a common side-effect and the ointment has been superceded by the imidazoles.
- **Imidazoles** These are all effective topically and should be applied once daily for 3 weeks. They are available over the counter.
- **Selenium sulphide shampoo** It is effective, but some patients do not like the smell and it may stain clothes. It should be applied once a week for 8 weeks but must be washed off after 5 hours to avoid irritation. Washing the hair with it as well may eliminate any fungus present in the scales of *pityriasis capitis*.
- **Oral therapy** It does not respond to griseofulvin and for this reason the alternative name *tinea versicolor* should be abandoned, for it gives a false impression. Itraconazole 200 mg daily for 5 days, is effective.

Pseudovitiligo

In those with pronounced hypopigmentation, the scaling (the sign of the active disease) disappears but white areas remain. The melanocytes take many months to recover and start producing pigment again. There is no way of speeding up repigmentation. Recurrences then occur in a minority, partly as a result of inadequate treatment (examination under a Wood's light often shows yellow fluorescence in parts that look macroscopically normal) and in sun worshippers.

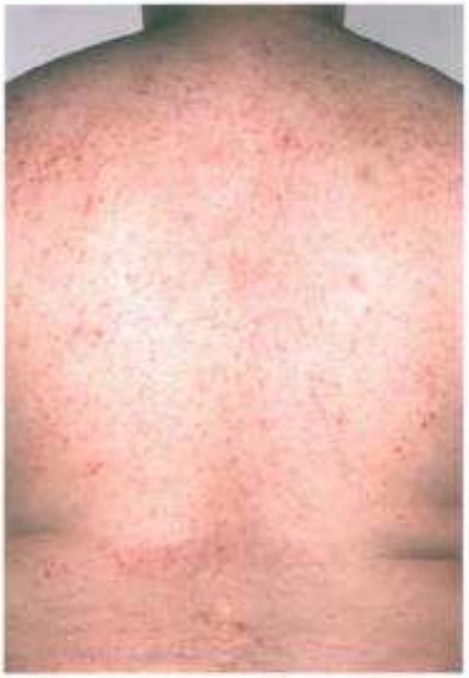


Fig. 15.23 Pityrosporum folliculitis. The condition is chronic and affects the torso. It appears like a mixture of acne and seborrhoeic dermatitis. *P. orbiculare* is present in the hair follicles.

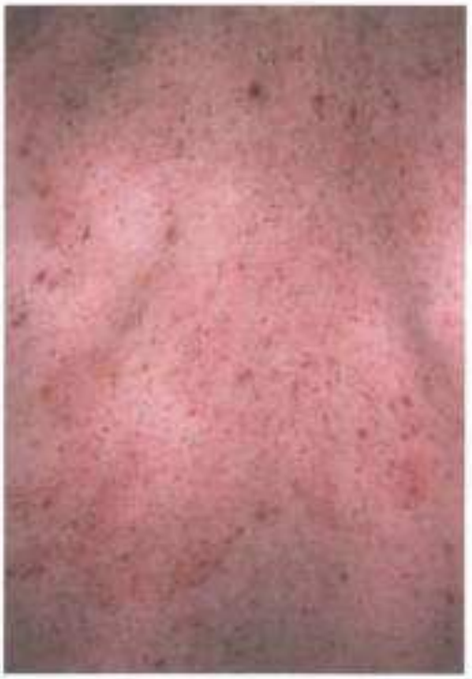


Fig. 15.24 Pityrosporum folliculitis. Discreet red papules and pustules are present. The condition responds to oral itraconazole and 13-cis-retinoic acid.

Pityrosporum folliculitis

An itchy follicular inflammation on the trunk caused by *Pityrosporum orbiculare*.

Aetiology

Pityrosporum species are found within the hair follicle, which is dilated, plugged with keratinous material and invaded by inflammatory cells. Oral ketoconazole was initially found to be effective, suggesting that the condition is caused by *Pityrosporum* species but relapses do occur. The condition is more common in males in the fourth decade and is often associated with a tendency to seborrhoeic dermatitis and alcohol misuse.

Clinical Features

Symptoms

In pityrosporum folliculitis there is an itchy rash on the torso (Fig. 15.23).

Morphology

Discrete erythematous follicular papules or pustules (Fig. 15.24).

Distribution

It occurs mainly on the upper trunk and shoulders.

Management

The *Pityrosporum* yeasts can be demonstrated on examination of scrapings treated with potassium hydroxide and in Gram stains of skin biopsies. The condition is often precipitated by tight-fitting clothing or antibiotic therapy.

- **Topical imidazoles** It does respond to some extent to these.
- **Systemic triazoles** These are effective although relapses occur.
- **Oral 13-cis-Retinoic acid** A course as given for acne may be curative.

Tinea (Ringworm)

'Tinea' is derived from the Latin word meaning clothes-moth, which the Romans thought was responsible for ringworm. It is caused, however, by superficial fungi (dermatophytes) that colonize keratin (hair, nails and the stratum corneum) but do not penetrate into the living cells. The fungus is a dermatophyte: a multicellular organism characterized by hyphae that mat together to form a mycelium. The hyphae (Fig. 15.25) can be visualized on direct microscopy of affected hair, nails or skin scales if treated with potassium hydroxide.

Various structures develop from the hyphae for propagation or perennation. The vegetative structures are known as chlamydospores and arthrospores. The latter are characteristic of the parasitic phase of the ringworm fungus. Numerous septa are formed to give chains of small cuboidal spores, with slightly thickened walls, which disarticulate when mature. Asexual spores may result from mitotic nuclear division. They are known as microspores (microconidia) and macrospores (macroconidia). They

Fig. 15.25 Dermatophyte hyphae. Hyphae are present in scrapings of skin treated with potassium hydroxide (×32). (Courtesy of Miss G. Midgley, Institute of Dermatology.)

may be carried endogenously within an envelope (sporangium), when they are known as conidiaspores (conidia). Dermatophytes are not recognized as reproducing sexually.

There are three relevant genera of dermatophyte: *Microsporum*, *Epidermophyton* and *Trichophyton*. They can only be identified on the basis of the morphology of their macroconidia (asexual spores), after 3–4 weeks on a culture medium. *Epidermophyton* conidia are smooth walled, relatively large and club shaped (clavate) (Fig. 15.26). The cell wall is intermediate in size. *Microsporum* macroconidia are rough walled, termed spiny or echinulate, and quite distinctive in appearance. They are spindle shaped and the cell wall is thick (Fig. 15.27). *Trichophyton* macroconidia are similar to *Epidermophyton* but may be cylindrical (Fig. 15.28), with a thin cell wall.

Dermatophytes may originate from the soil (geophilic), from animals (zoophilic) or from humans (anthropophilic). Geophilic fungi, for example *Microsporum gypseum*, only sporadically infect humans. Zoophilic fungi produce an inflammatory, often suppurative, infection in humans but may be clinically silent in animals. Infection may arise from direct contact or indirectly, via clothing or other inanimate materials contaminated with infected animal hair. The exposed parts, namely the scalp, beard, face and arms, are most usually affected. Animal ringworm produces so much inflammation that second attacks are rare. Thus American troops in Vietnam were severely disabled and incapacitated by animal species of *T. mentagrophytes*, whereas their South Vietnamese comrades were not, presumably because they had acquired immunity as children. Human infections are relatively non-inflammatory, tend to involve covered areas (for example, feet and groin) and are often well tolerated by the host (especially *T. rubrum*).

Host factors are important. Impaired cell-mediated immunity predisposes to these infections. Children are susceptible to scalp ringworm whereas adults rarely are. Black children are particularly prone to epidemic human forms. Males have a higher incidence of tinea, probably because females tend to have less exposure to sporting facilities and institutions where tinea is rife.

Tinea infections often result from damage to the stratum corneum. Occlusion increases the local temperature and hydration of the skin, leading to impaired barrier function. This probably explains why tinea pedis is a disorder of the shod and not those who go barefoot. Shoes made of non-porous materials are associated with an increased incidence of infection. Tinea cruris and pedis are common throughout the world. They are caused by anthropophilic fungi only, particularly *Epidermophyton floccosum*, *T. rubrum* and *T. mentagrophytes* var. *interdigitale*. They are most prevalent in the tropics, because the warm, humid conditions promote growth. *T. rubrum* was imported into the UK by troops who served in the East during World War II.

T. rubrum (Fig. 15.29) is the commonest cause of dermatophytosis. *T. mentagrophytes* is also common. It may affect both humans and animals.

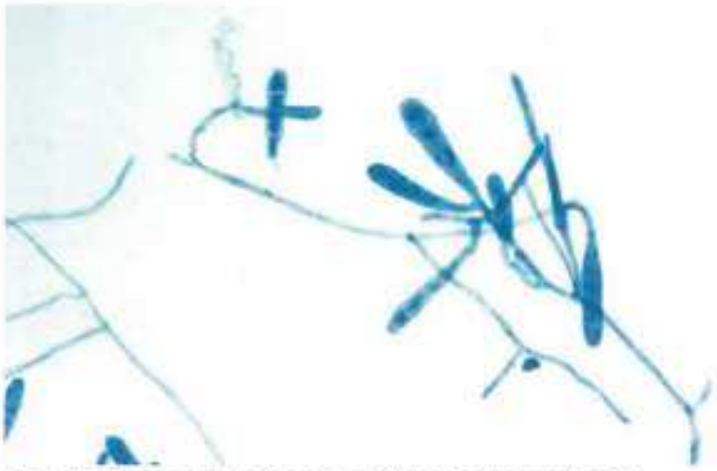


Fig. 15.26 *Epidermophyton floccosum*. The conidia are smooth walled, relatively large and club shaped (clavate). (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

Fig. 15.27 *Microsporum canis*. The macroconidia are spindle shaped. The cell wall is thick and spiny (x10). (Courtesy of Dr Y. M. Clayton.)

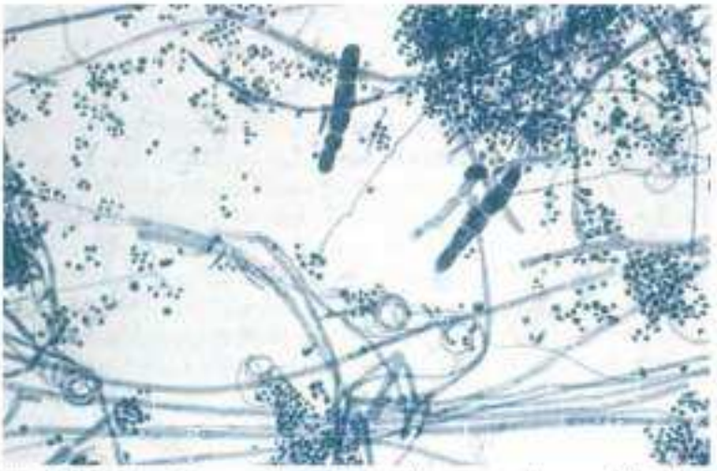


Fig. 15.28 *Trichophyton mentagrophytes*. The macroconidia are cylindrical. (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

Fig. 15.29 *Trichophyton rubrum*. The underside of the plate is a red colour, hence the adjective *rubrum*. It is the most common cause of dermatophyte infections in the UK. (Courtesy of Dr Y. M. Clayton.)

Fig. 15.30 *Trichophyton mentagrophytes* var. *interdigitale*. The colonies are creamy and powdery. (Courtesy of Dr Y. M. Clayton.)

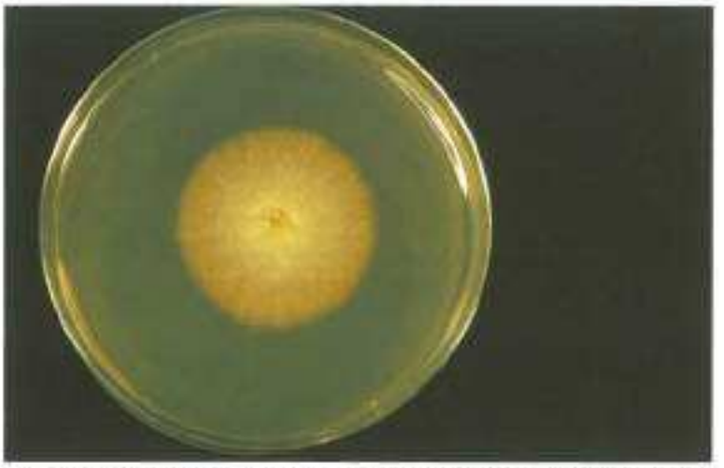


Fig. 15.31 *Epidermophyton floccosum*. A khaki or olive-green powdery colony forms on culture. (Courtesy of Dr Y. M. Clayton.)

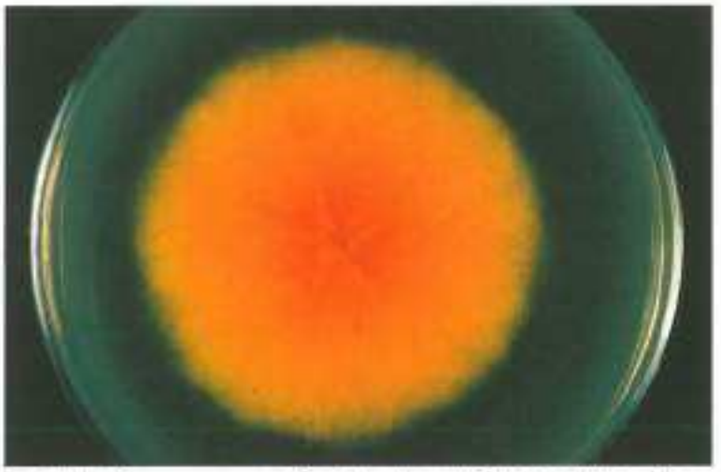


Fig. 15.32 *Microsporum canis*. On culture, the underside of the plate is yellow. (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

Fig. 15.33 *Trichophyton verrucosum*. Small discrete white glabrous colonies are present. They grow best at 37°C. (Courtesy of Dr Y. M. Clayton.)

The anthropophilic variant *T. mentagrophytes* var. *interdigitale* produces a 'downy' appearance on culture (Fig. 15.30). The zoophilic variant is granular and is known as *T. mentagrophytes* var. *mentagrophytes*. *E. floccosum* produces khaki or olive-green powdery colonies on culture (Fig. 15.31).

TINEA CAPITIS

A common childhood infection with anthropophilic or zoophilic dermatophytes that can invade either the inner or outer part of the hair shaft.

Aetiology

Scalp ringworm is more common in lower socioeconomic groups, conditions of overcrowding and poor hygiene. It can be transmitted by shared brushes, combs, hats, pillowcases and contaminated barber's equipment. Some species are ubiquitous but others have a relatively limited geographical distribution. It is rare after puberty (except *T. tonsurans* infections) probably because sebum contains saturated fatty acids, which are hostile to the fungus. Indeed the fatty acid undecenoic acid is an effective topical remedy. Also some hair oils are inhibitory, and societies that use them routinely are far less prone.

The physical signs are determined by the source of infection and the mode of invasion of the hair. Human infections produce quite minor degrees of erythema and scaling, but animal infections induce considerable inflammation because the host resistance is usually high. This may result in a boggy mass of inflamed and purulent skin known as kerion. Certain fungi invade the outer root sheath of the hair, so giving the hair a rather dull appearance and causing it to break off above the scalp surface. These are known as ectothrix fungi. Other fungi invade the inner hair shaft and produce more pronounced damage; in these infections the hairs are broken off close to the surface of the scalp. These are known as endothrix fungi. Scalp ringworm infections are traditionally classified as ectothrix and endothrix infections, kerion and favus, respectively. Only *Microsporum* and *Trichophyton* species are responsible.

Fig. 15.34 *Trichophyton violaceum*. Violet waxy colonies grow. The fungus is common in the Mediterranean and Indian subcontinent. (Courtesy of Dr Y. M. Clayton.)

Fig. 15.35 *Trichophyton tonsurans*. Buff-coloured folded powdery colonies are visible. (Courtesy of Dr Y. M. Clayton.)

Fig. 15.36 Small-spored ectothrix. Infection of the outer hair root sheath is caused by *Microsporum* species, as shown in this 30% potassium hydroxide preparation (×32). (Courtesy of Miss G. Midgley.)

Fig. 15.37 Endothrix infection. The fungus invades the inner hair shaft as shown in this 30% potassium hydroxide preparation (×96). (Courtesy of Miss G. Midgley, Institute of Dermatology.)

The most common species infecting the scalp in the UK were *Microsporum canis* and *Microsporum audouinii* and still are in Central Europe. The former is zoophilic from a puppy or kitten; the latter is anthropophilic. The fungus first invades the stratum corneum of the scalp and then the outer root of the hair, coating it with spores. These fluoresce bright green under the Wood's light, which is a rapid means of screening children for *Microsporum* infection. *M. canis* (Fig. 15.32) and *M. audouinii* are distinguishable on culture in that the former grows on polished rice and the latter does not. In addition *M. audouinii* produces a characteristic salmon-coloured pigment on potato dextrose agar and has a unique feature of comb-like (pectinate) projections on the hyphae. The main cause of scalp ringworm in the USA is now *T. tonsurans* (imported from its southern neighbours) and in the UK from Africa. *T. violaceum* is most common in Australia and Western Southern Asia.

The animal fungi *T. verrucosum* (Fig. 15.33) and *T. mentagrophytes* var. *granulare* may cause tinea capitis. Both infect cattle and horses, and the latter infects rodents; therefore a pet may be the source. These species of fungus do not fluoresce under the Wood's light.

Endothrix infections are all anthropophilic. They are *T. soudanense* (Africa), *T. violaceum* (Fig. 15.34) (Mediterranean, Central Europe, Russia, North Africa), *T. tonsurans* (Fig. 15.35) or *T. sulphureum* (both worldwide, but especially North and Middle America) and *T. schoenleinii* (Middle East, Eastern Europe, Mediterranean and South Africa). *T. soudanense* infection of hair fluoresces a dull bluish-white colour on Wood's light testing. Favus, caused by *T. schoenleinii*, produces a distinctive dull blue-green fluorescence of the hair. It may result in a scarring alopecia and is characterized by the presence of arthroconidia and air spaces within the hair shaft.

Clinical Features

Symptoms

There are one or more patches of hair loss.

Morphology

The morphology varies with the fungus, and particularly ectothrix (Fig. 15.36) or endothrix (Fig. 15.37).

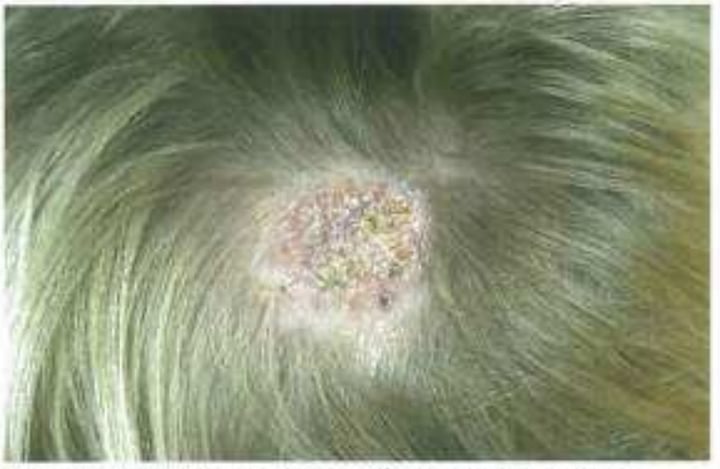


Fig. 15.38 Tinea capitis. The condition affects children. In anthropophilic infections, there are patches of hair loss with minimal scaling.

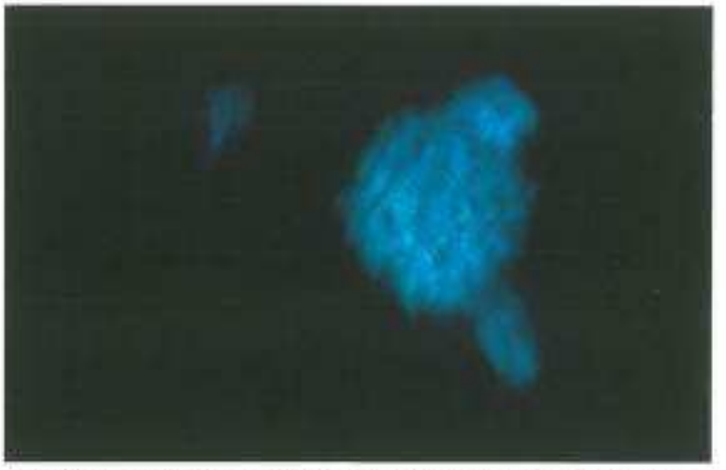


Fig. 15.39 Wood's light fluorescence. *Microsporum* hair infections fluoresce under Wood's light. This is helpful in identifying affected children in epidemics. (Courtesy of Dr Y. M. Clayton, Institute of Dermatology.)

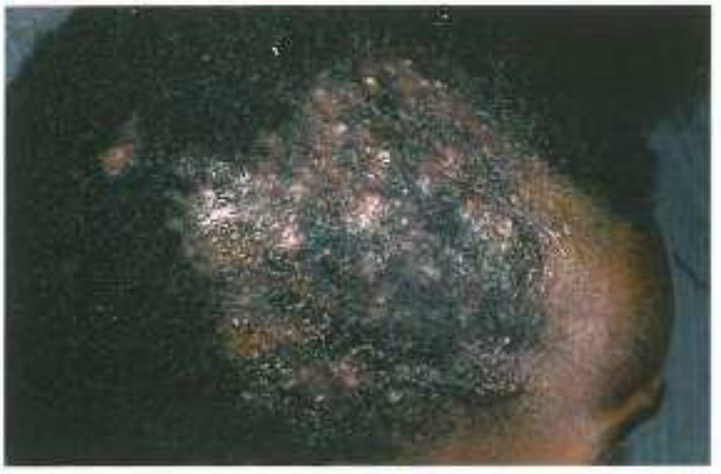


Fig. 15.40 Kerion. There is a boggy mass surmounted by pustules leading to weeping and crusting and diffuse hair loss. This was caused by *Microsporum canis* from an infected kitten.

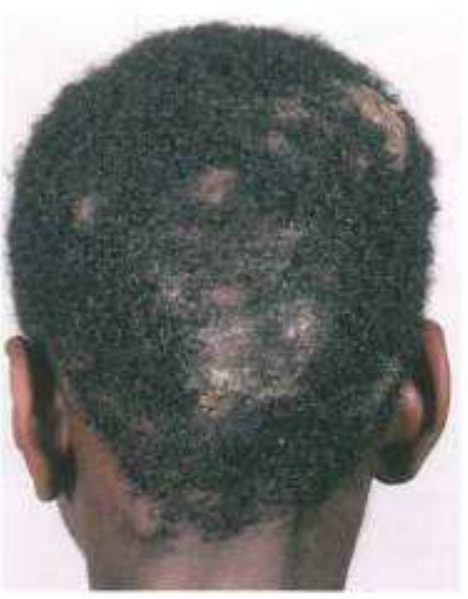


Fig. 15.41 Kerion. There are extensive patches of alopecia and a severe inflammatory reaction. Note his enlarged left-sided occipital lymph node.

- **Human epidemic species** The non-inflammatory epidemic human species *M. audouinii* produces scaling with minimal inflammation of the scalp. It starts as a small, red papule that surrounds the hair shaft; it then spreads centrifugally and gives rise to well-demarcated patches (Fig. 15.38). These may spread from the occiput onto the posterior neck. The affected hairs are grey and lustreless from the coating of spores and break off just above the level of the scalp. These fluoresce green under a Wood's light (Fig. 15.39).
- **The zoophilic fungi** These produce a pustular folliculitis that may develop into a *kerion*, an inflammatory boggy mass (Fig. 15.40), studded with broken hairs, which oozes purulent material from the follicular orifices. It is itchy and sometimes painful; occasionally there is fever and lymphadenopathy (Fig. 15.41). *T. tonsurans* is the commonest cause of kerion, particularly in black patients. Occasionally, a diffuse morbilliform Id reaction is associated with a kerion.
- **Endothrix infections** These attack the hair shaft, making it so brittle that it breaks off at the level of the scalp. Initially there may be a dry seborrhoeic-like scaling (Fig. 15.42) and only slight loss of hair. As the hair follicle becomes invaded, there is increased hair loss and black dots, which represent the remains of the hairs, are seen (Fig. 15.43). A pattern of patchy baldness and minimal scaling may be all that is found on examination. If misdiagnosed as seborrhoeic dermatitis or cradle cap and treated with topical steroids, the condition becomes extensive (Fig. 15.44).
- **Favus** In favus, characteristic yellow crusts or mats of hyphae (scutula; Fig. 15.45) occur around the hair follicles, although these are not always present. The hyphae are not as abundant as in other endothrix infections and so the hair is not as damaged and may grow to some length. There is a characteristic mousy odour associated with this condition. Neglect may lead to permanent scarring alopecia.

Fig. 15.42 Tinea capitis. There may be a dry seborrhoeic-like scaling with only slight hair loss. It may be spread by contaminated barber's instruments and is common in shaven scalps.

Fig. 15.43 Black dot endothrix infection. Endothrix infections make the hairs break off and black dots representing the remains of the hair may be all that is seen. (Courtesy of Dr Claire Fuller.)

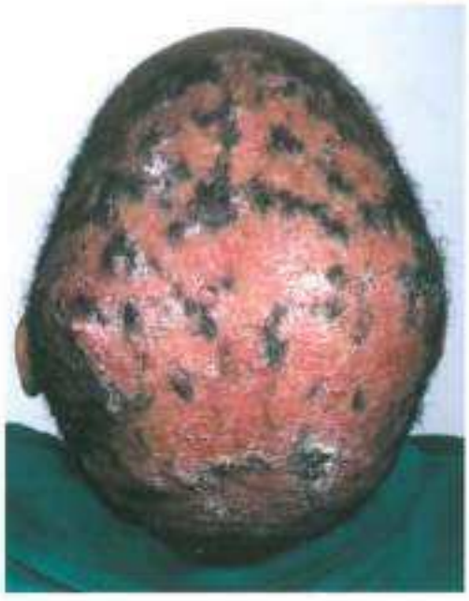


Fig. 15.44 Tinea capitis. This 2-year-old's tinea capitis was misdiagnosed as 'cradle cap' and treated with topical steroids, which inevitably exacerbated the condition by virtue of their immunosuppressive effects.

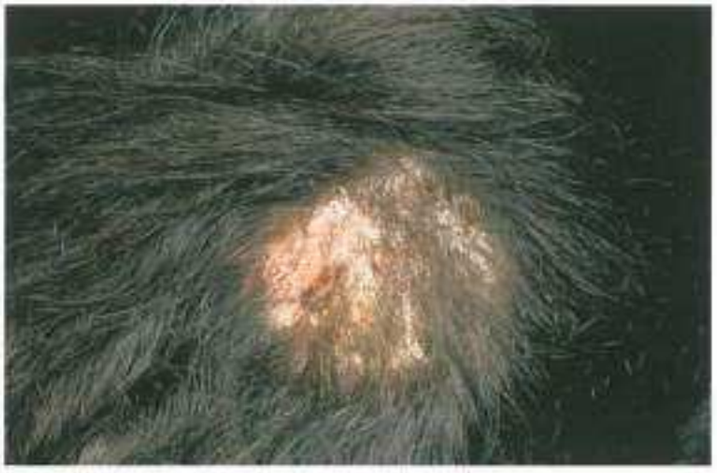


Fig. 15.45 Favus. Yellow crusts or mats of hyphae (scutula) occur around the hairs. (Courtesy of St John's Hospital for Diseases of the Skin.)

Diagnosis

Hair should be plucked and scales taken from the affected areas. The fungus may be seen under the microscope after the specimens have been treated with potassium hydroxide, but some experience is required. Specimens may also be taken by brushing the scalp and hair vigorously with a toothbrush, and impressing the bristles into a Sabouraud's plate.

Both *Microsporum* species fluoresce a brilliant green under the Wood's light. In an outbreak at a school, a Wood's light can be used to screen all the children, thus controlling a potential epidemic.

Prior to the availability of griseofulvin in 1959, the condition was chronic and did not clear until puberty. X-ray epilation of affected hairs was the only effective treatment. Regrettably, many children were over-irradiated and permanent (Fig. 15.46), rather than temporary, loss of hair resulted, secondary to scarring. Some of these patients are still alive and are at risk of developing malignant tumours of the skin in the irradiated areas.

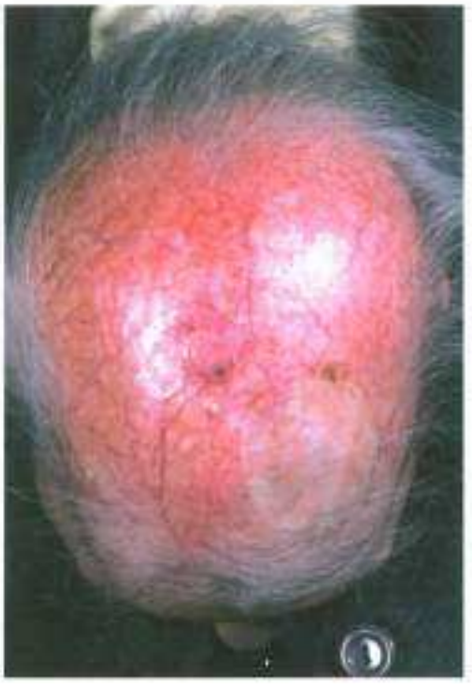


Fig. 15.46 Alopecia secondary to irradiation of scalp ringworm. The skin is atrophic and telangiectasia is obvious (radiodermatitis). He was 88 and had had radiotherapy 80 years previously, and had been bald ever since. A skin graft is present from excision of a squamous cell carcinoma.

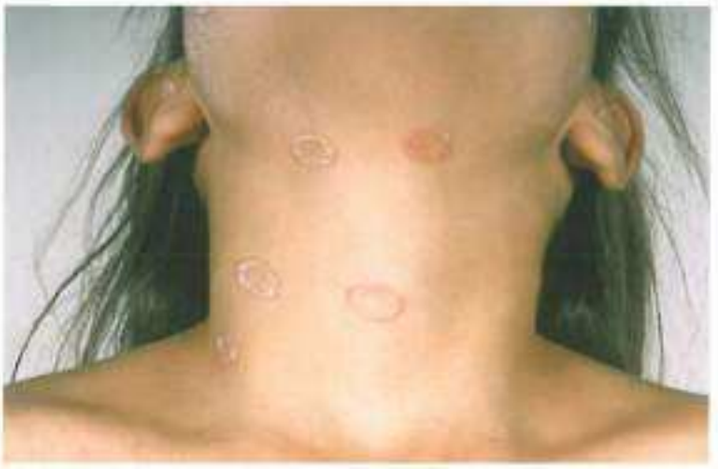


Fig. 15.47 Tinea corporis. This is classical annular ringworm in a child; there is a well-defined red scaly margin, which contrasts with a healing centre.

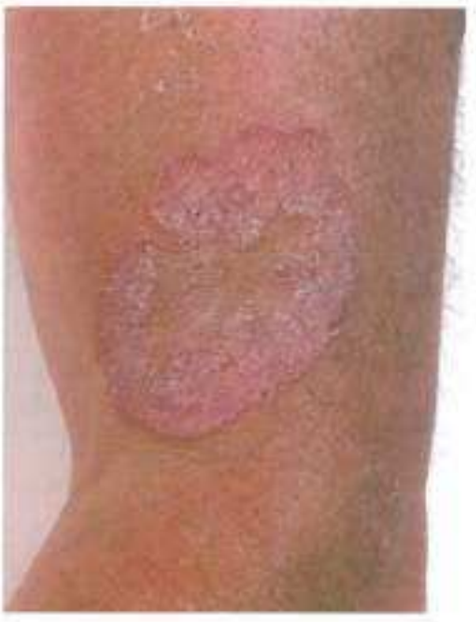


Fig. 15.48 Tinea corporis. The margin of the ringworm lesion is the most active, with a tendency for central healing.

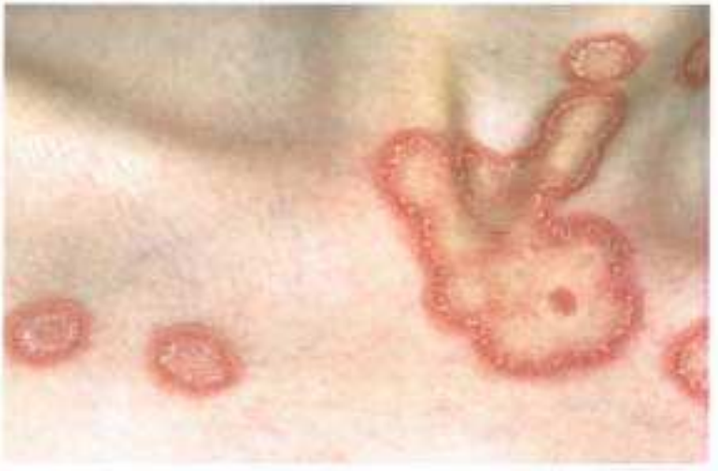


Fig. 15.49 Tinea corporis. The margin is very inflamed; this was an infection with *Microsporum canis* from a puppy.

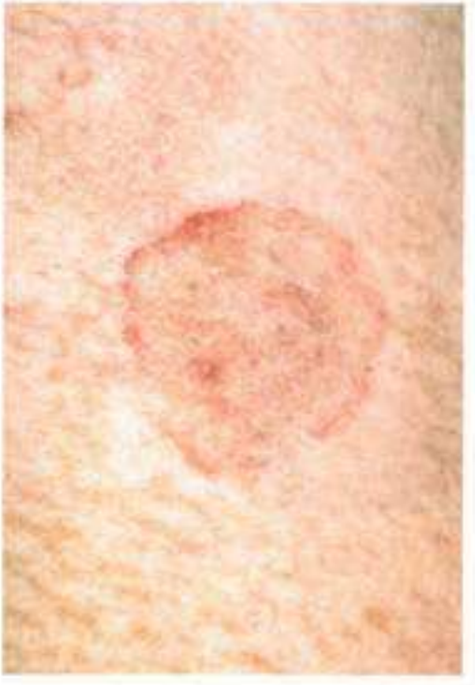


Fig. 15.50 Tinea corporis. The margin in 'ringworm' is most active, with a tendency to central healing and pigmentation.

TINEA CORPORIS

An infection of glabrous (smooth) skin, that may be caused by any of the dermatophytes, often colloquially known as ringworm.

Aetiology

Tinea corporis may be caused by *Epidermophyton Floccosum*, *Microsporum* or *Trichophyton* species. It may be spread onto glabrous skin from the scalp (Fig. 15.47) or, in the case of *T. rubrum*, from the feet and groin. Tinea corporis is also contracted from animals including cattle, horses, puppies, kittens and small rodents kept as pets. *T. imbricata*, an anthropophilic dermatophyte found in southeast Asia and parts of the Southern Americas, produces a rather distinctive concentric pattern.

Clinical Features

Symptoms

An itchy ring-shaped rash.

Morphology

The fungus tends to grow outwards. Therefore, the margin is most active. It is well-defined (Fig. 15.48), slightly raised, red and scaly, and if the source is an animal, may be quite inflamed (Fig. 15.49) and even pustular. Centrally, there is a tendency to healing and postinflammatory hyperpigmentation (Fig. 15.50).

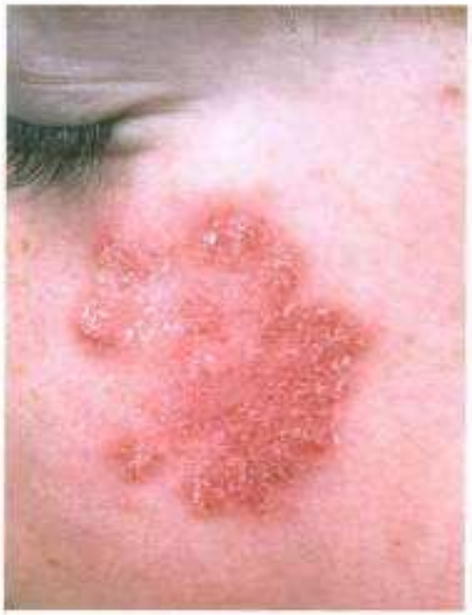


Fig. 15.51 Tinea facei. Tinea may be quite inflammatory if from a zoophilic species. Note that the margin is more raised and scaly and that there is central healing.

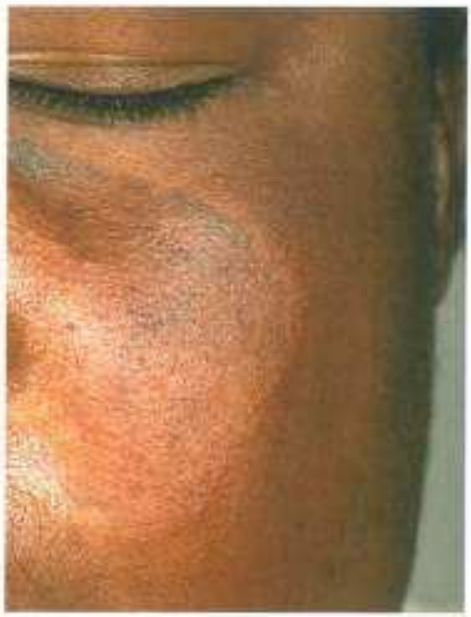


Fig. 15.52 Tinea facei. The annular nature of the rash should suggest the diagnosis and need for microscopy.

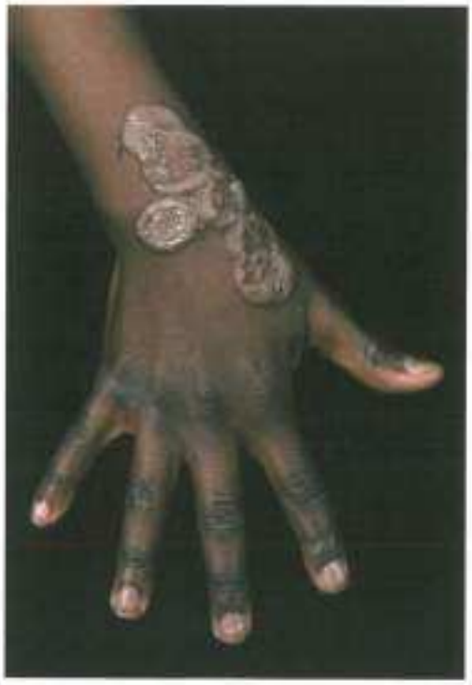


Fig. 15.53 Tinea corporis. These annular bullous lesions were caused by *T. tonsurans*. Although mistaken for impetigo, the lesions contained turbid but not yellow fluid.

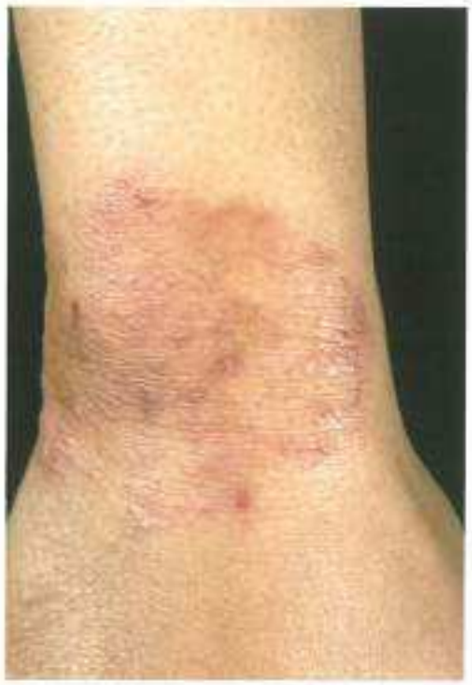


Fig. 15.54 Tinea corporis. Occlusion favours the growth of fungal disorders. Tinea under the watchstrap is often misdiagnosed as eczema.

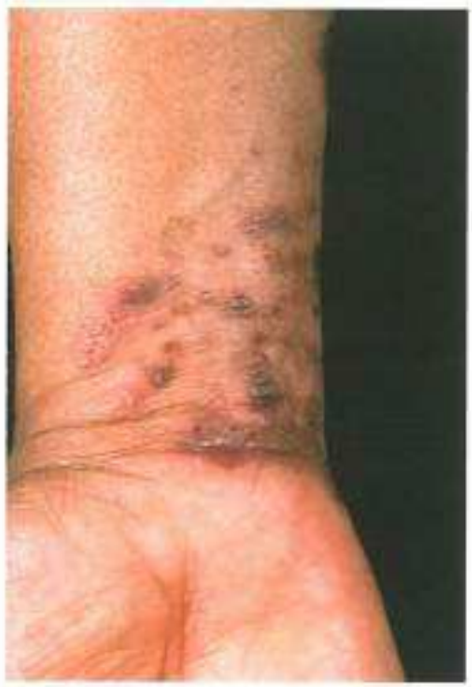


Fig. 15.55 Tinea incognito. Steroids are anti-inflammatory and immunosuppressive. They permit dermatophytes to flourish. The rash is annular. Pigmentation is prominent but redness and scaling are visible.

Distribution

The patches may be single or multiple, are scattered asymmetrically and may occur anywhere on the body, but particularly on the trunk and limbs.

Two sites cause diagnostic problems. These are the face, including the beard area, and under the watchstrap. Tinea on the face (Figs 15.51 and 15.52) is often misdiagnosed as eczema. Animal ringworm and *T. tonsurans* are often inflammatory and even bullous and misdiagnosed as herpes simplex or impetigo (Fig. 15.53), and tinea under the watchstrap (Fig. 15.54) as metal sensitivity and treated with steroids (Fig. 15.55).

It is always worth examining all the skin when faced with a difficult diagnosis. The presence of fungus between toes or in the groin may indicate the source of tinea corporis.

The name of ringworm is misused so often that it is appropriate to consider other annular eruptions that are frequently mistaken for tinea.

- **Discoid eczema** The redness and scaling occurs uniformly across the lesion and there is no central healing or preferential peripheral activity.
- **The herald patch of pityriasis rosea** The lesion is pink throughout and has a collarette of scale towards, but not at, the periphery.
- **Granuloma annulare** The pathology of this condition is in the dermis. There is no epidermal component, so there will be no scaling.

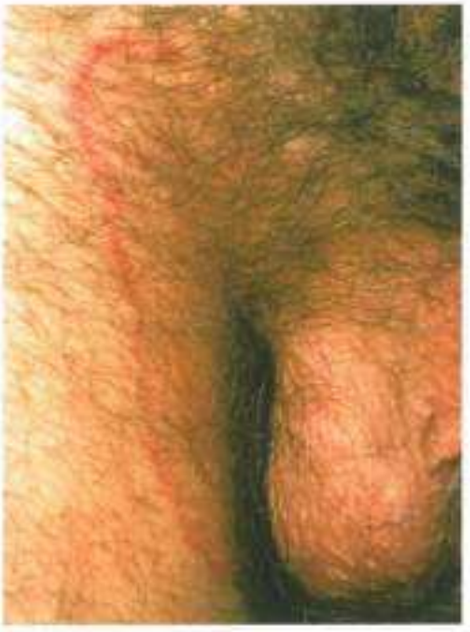


Fig. 15.56 Tinea cruris. The margin of the eruption is red and scaling and tends to advance away from the genitocrural fold down the inner thigh. (Courtesy of the Institute of Dermatology.)

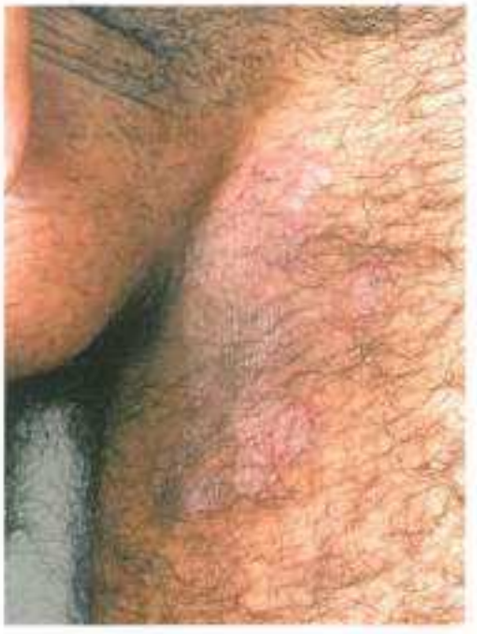


Fig. 15.57 Tinea cruris. The redness and scaling spreads away from the groin down the inner thigh.

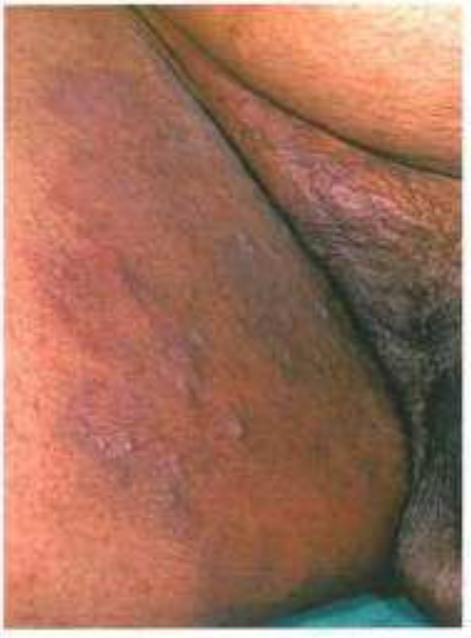


Fig. 15.58 Tinea incognito. The usual physical signs are masked and the eruption is often pustular in amongst a diffuse erythema and pigmentation.

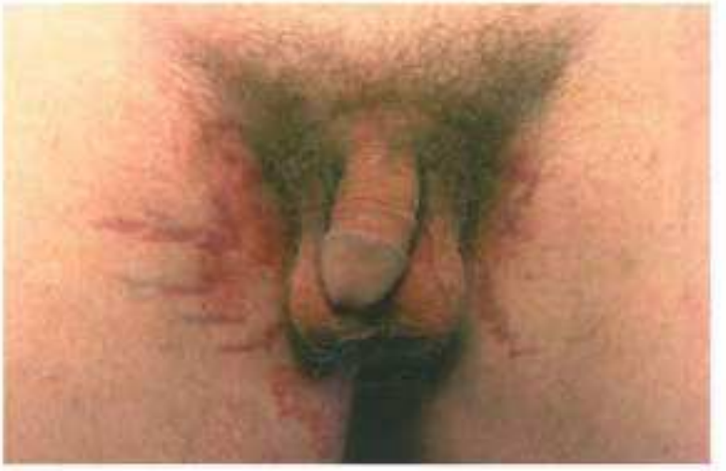


Fig. 15.59 Tinea incognito. Gross striae have resulted from powerful topical steroids. The inflammatory physical signs are suppressed except on the lower part of his right inner thigh, where the patient had not applied the steroid. (Courtesy of the Institute of Dermatology.)

TINEA CRURIS

Tinea cruris is an infection of the groin by an anthropophilic dermatophyte.

Aetiology

Tinea cruris (Dhobi itch) is usually caused by one of the three anthropophilic species involved in tinea pedis. *T. rubrum* is the commonest cause but *E. floccosum* and *T. mentagrophytes* var. *interdigitale* may also be responsible. It particularly affects males.

Clinical Features

Symptoms

An itchy rash in the groin spreading often onto the buttocks.

Morphology

The rash is red and scaly (Fig. 15.56), particularly at the margin, which is very slightly (Fig. 15.57) raised.

There is a tendency in tinea cruris for the lesions to show central clearing and postinflammatory pigmentation. If the patient has been treated with topical steroids up to the time of the consultation, the edge may be non-existent and the eruption may appear just as a diffuse erythema or scaling; if treatment has been abandoned for a few days, the edge may be quite inflamed and pustular (Fig. 15.58). If powerful steroids have been used for a long time, atrophy and striae result (Fig. 15.59).

Distribution

The fungus spreads asymmetrically on both sides of the inner thighs, downwards and away from the genitocrural folds; as a result, the scrotum is rarely involved. It may spread onto the buttocks (Fig. 15.60).

Diagnosis

Scrapings should be taken of the skin and examined microscopically in potassium hydroxide or sent to the laboratory. The feet and toenails should be examined because this may be the source of the infection. The differential diagnosis includes *C. albicans* infection (Fig. 15.61), erythrasma (Ch. 13), psoriasis (Fig. 15.62) or seborrhoeic eczema (Ch. 3).

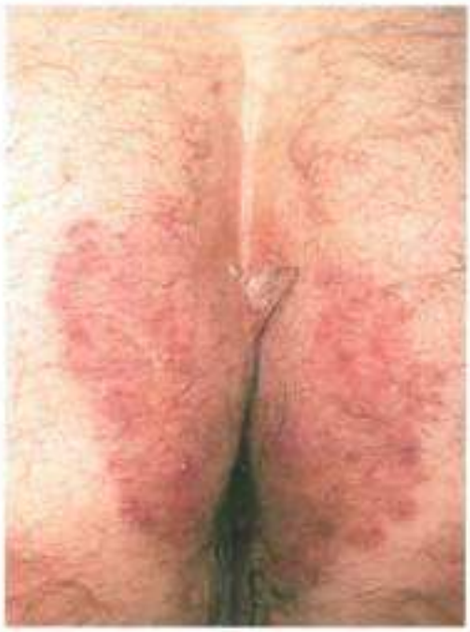


Fig. 15.60 Perianal tinea. The dermatophyte may spread from the feet to the groin, buttocks and perianal area. The margin is well defined.

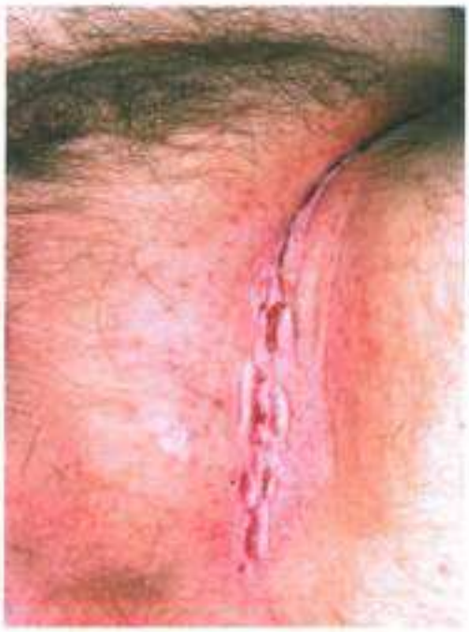


Fig. 15.61 Candida albicans. There is maceration (a white sodden appearance of the skin) in the intertriginous fold with satellite pustules. A swab should be taken to confirm the diagnosis and diabetes and other causes of immunosuppression be ruled out.

Fig. 15.62 Psoriasis. Psoriasis is symmetrical and uniformly red. Tinea is unilateral or asymmetrical with scaling at the margin and central healing.

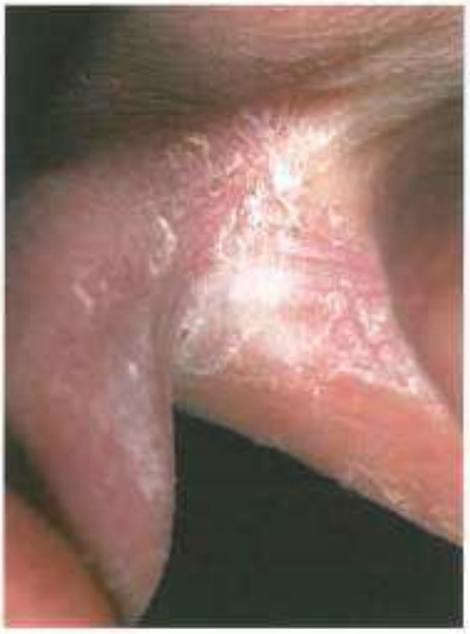


Fig. 15.63 Tinea pedis. There is peeling, maceration and fissuring in the toe clefts.

TINEA PEDIS

A fungal infection of the skin of the feet and sometimes the toenails.

Aetiology

T. rubrum and *E. floccosum* cause the moccasin type, *T. mentagrophytes* var. *interdigitale* and *E. floccosum* the interdigital type, while *T. mentagrophytes* var. *mentagrophytes* usually cause the inflammatory variety. It begins in the toe webs. There is maceration, peeling and erythema, usually in the lateral toe webs, which may spread to involve the undersurface of the toes and soles and rarely the dorsa of the feet.

Clinical Features

Symptoms

It is pruritic and may be sore if the eruption is fissured. It is usually asymmetrical, with one foot more heavily involved, which distinguishes it from endogenous disorders such as psoriasis.

Morphology

Tinea pedis may behave in a number of ways.

- **Interdigital type** There is peeling, maceration and fissuring in the lateral toe clefts (Fig. 15.63), which often spreads to involve the undersurface of the toes. It may be quite itchy in warm weather.

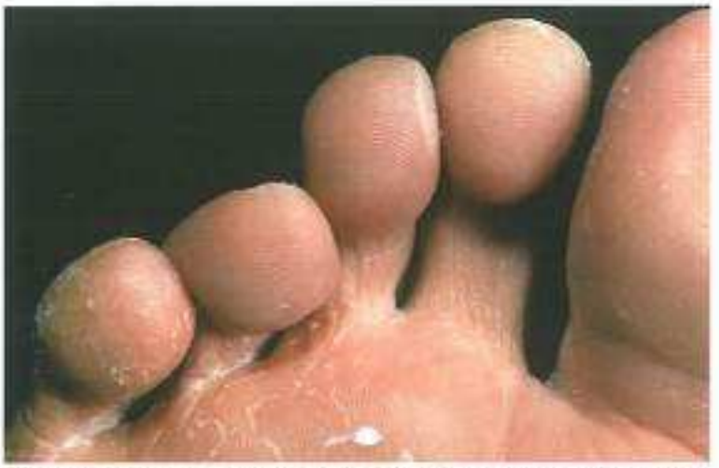


Fig. 15.64 Tinea pedis. The skin is dry and powdery. There is peeling of the skin with quite characteristic crescentic scales.

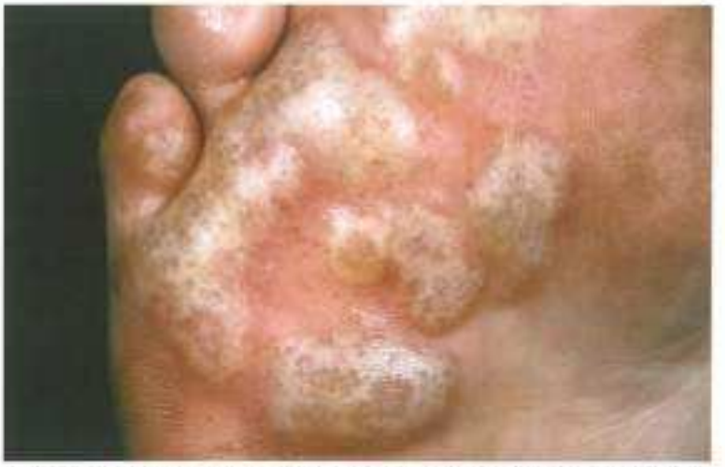


Fig. 15.65 Acute tinea pedis. Tinea may present as vesicles on the sole of the foot. The eruption is usually unilateral.

- **Chronic tinea pedis** The skin is dry and powdery, with some peeling and the production of crescentic scales (Fig. 15.64). The condition is sometimes referred to as the moccasin type because of its distribution. It is insidious in its evolution and is usually caused by *T. rubrum*, although *E. floccosum* may also be responsible. Neither produces much host response. The nails are frequently involved when *T. rubram* is responsible.
- **Acute tinea pedis** Vesicles develop that coalesce to form frank blisters (Fig. 15.65). The eruption is usually unilateral (which distinguishes it from a pompholyx). A lymphangiitis with lymphadenopathy may occur. The condition is most commonly caused by *T. mentagrophytes* var. *interdigitale*, but sometimes by *E. floccosum*. This variety may give rise to the *dermatophytid reaction*. Although not common, this reaction is a bilateral, symmetrical, vesicular pompholyx that develops on the palms of the hands as a result of a severe fungus infection on the foot. No fungi are isolated from the skin of the hands, however, and it is considered to be a secondary allergic reaction to the fungus on the foot. This Id phenomenon responds to topical steroids for the palms and antifungals for the foot.
- **Tinea pedis treated with topical steroids** If tinea pedis is misappropriately treated with topical steroids, it spreads onto the dorsa of the feet to produce an eruption with an active, slightly raised, scaly margin (Fig. 15.66).
- **Gram-negative toe web infections** The condition is most common in patients who use germicidal soaps and those with tinea pedis. However, dermatophytes can only be cultured in about a third of cases, possibly because they produce antibiotics that select for lipophilic diphtheroids which acquire resistance. The condition, therefore, probably represents bacterial overgrowth after a primary fungal infection. The second, third and fourth webs are usually affected. There is denudation of the interdigital skin with a serous or purulent discharge, which may be green (see Fig. 13.38) because of the release of pyocyanin. The interdigital spaces are white, macerated, eroded, fissured and soggy. There is an odour, pruritus and discomfort. The condition responds to a combined approach of topical antifungal and appropriate antibiotics.

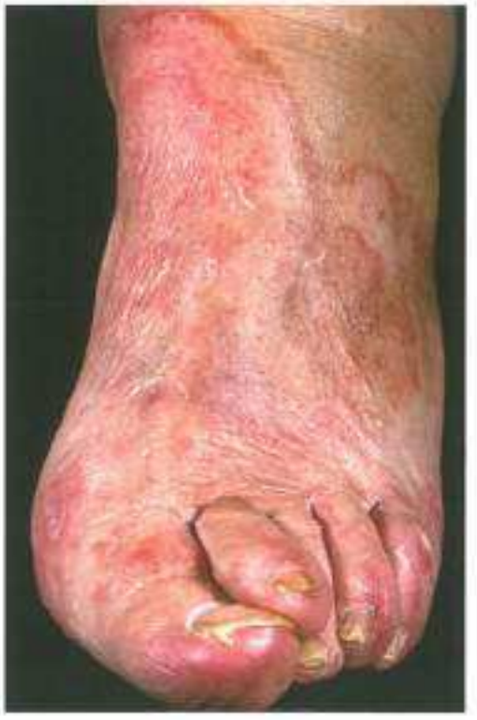


Fig. 15.66 Tinea pedis treated with steroids. There is a well-defined red margin and concentric rings within it. Note the involvement of the toenails.

TRICHOPHYTON RUBRUM HAND INFECTIONS

Involvement of the palm and fingernails on one hand by *T. rubrum* associated with infection in both feet and toenails.

Aetiology

When *T. rubrum* affects one hand, it hardly ever spreads to the other despite the involvement of both feet, toenails and groin. This bizarre phenomenon has not been satisfactorily explained.

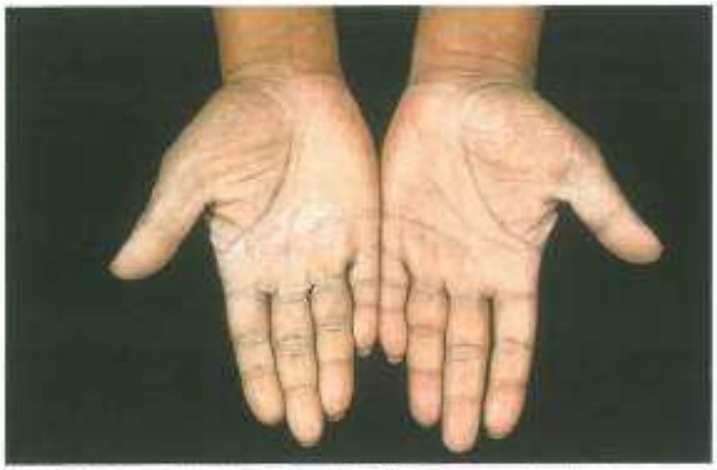


Fig. 15.67 Tinea of the hand. Fungal infections have a predilection for one hand only, with sparing of the other. The skin creases of his right hand are filled with a fine powdery scale.

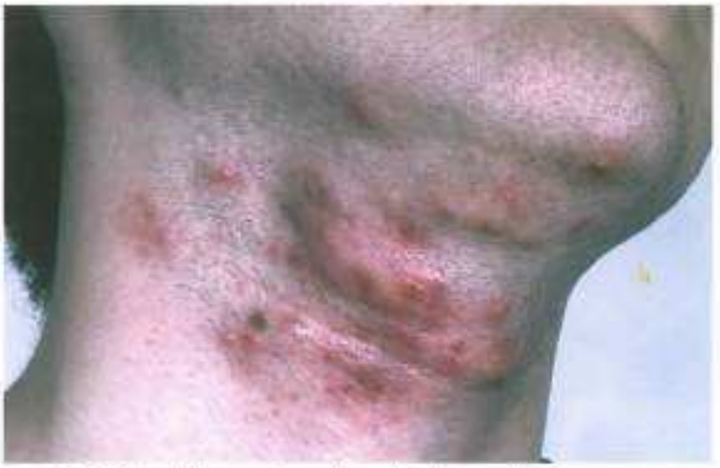


Fig. 15.68 Majocchi's granuloma. A granulomatous reaction may occur as multiple dusky red nodules that fluctuate and occasionally ulcerate. This was caused by *Trichophyton mentagrophytes*.

Clinical Features

Symptoms

The palmar skin of one hand feels very dry and there is scaling.

Morphology

There is a powdery filling-in of the skin creases and crescentic peeling scales are present.

Distribution

One hand is affected (Fig. 15.67) by *T. rubrum* and often the fingernails become involved in that hand in an asymmetrical manner. The feet and toenails are invariably involved at an earlier stage.

Management of Tinea

The diagnosis may be established by scraping the skin with a blunt scalpel and taking clippings from the nails if they are involved. In acute tinea pedis, it is useful to remove the skin of the roof of a blister with a pair of scissors. These specimens may be treated with potassium hydroxide and examined for hyphae under a microscope or sent to the laboratory for culture. Biopsy is rarely required; however, when the diagnosis is not suspected by the clinician it may be established by the pathologist. This may occur in *Majocchi's granuloma*, which is secondary to *T. rubrum* infection and manifests as multiple dusky red nodules that fluctuate (Fig. 15.68) and may occasionally ulcerate. This is seen in the immunocompromised but particularly those who have been treated with topical corticosteroids. A second type is of small perifollicular papules, which are seen in females who shave their legs or under the maceration and trauma caused by a tight-fitting wrist watch. Although most patients are otherwise perfectly healthy, immunosuppressed patients are prone to fungal infections (Fig. 15.69).

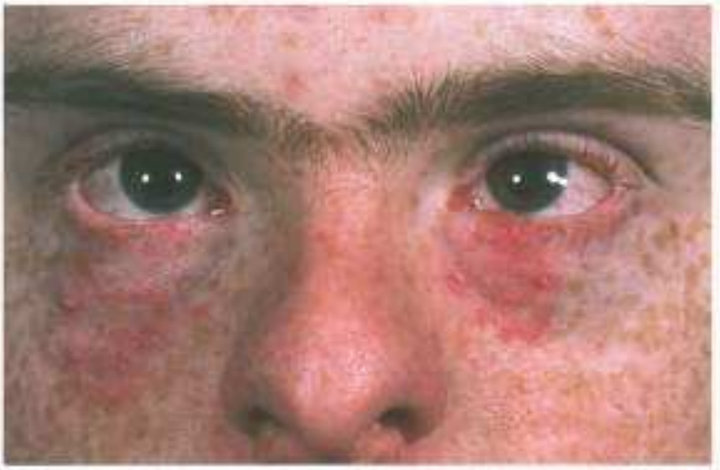


Fig. 15.69 Tinea facei in Down's syndrome. Immunosuppressed patients including those with Down's syndrome are more vulnerable to fungal infections. The lesions under the eyes have a pronounced red margin.

Topical therapies

There are various topical remedies. Half-strength Whitfield's ointment, undecenoic acid and tolnaftate are helpful but the imidazoles are now the most commonly used. Castellani's paint, with or without the magenta, and potassium permanganate soaks (1:10 000) are helpful in acute vesicular tinea pedis. The foot is soaked for 10 minutes once or twice a day, then dried and treated with an imidazole cream. The patient should be warned that the soak stains the skin and browns the nails temporarily.

Topical therapy on its own is of little avail in tinea capitis.

A common error is to treat tinea, especially in the groin, with a combined steroid, antibacterial/antifungal drug. Most of these, for example Tri-Adcortyl (Mycolog, USA) contain nystatin as the antifungal, which has no effect against tinea. The preparation, therefore, only worsens the situation because of its steroid effect. There is also a tendency to use combined imidazoles/hydrocortisone preparations in the groin: the imidazole is effective against tinea but is in danger of being counterbalanced by the steroid. There is no need for steroid combinations, even in very inflammatory ringworm, for the condition responds to oral terbinafine. However, if there is doubt about the diagnosis, one of these preparations is permissible until the result of the scrapings is available.

Systemic therapies

The indications for systemic therapy are:

- acute infections
- scalp infections
- nail infections
- *T. rubrum* infections
- tinea incognito.

The drugs which are available are:

- **Griseofulvin** This has a long and established safety record. The most common minor side-effects are nausea and a short-lived headache. It is occasionally a photosensitizer and sometimes causes a fixed drug

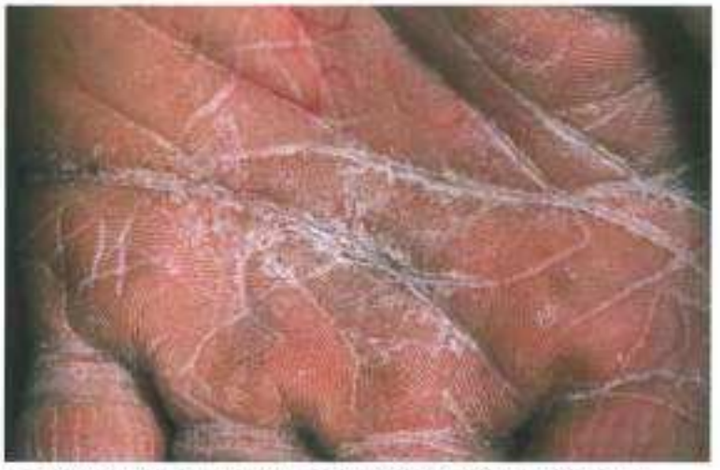


Fig. 15.70 *Scytalidium hyalinum*. Both palms are involved. The scaling is prominent in the creases, as in this West Indian. Caucasians do not appear to be affected.

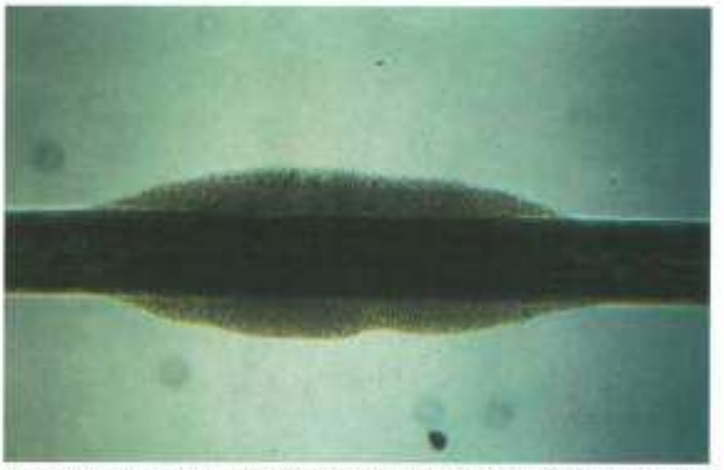


Fig. 15.71 Piedra blanca. Soft white or light brown nodules are seen attached to the hair shaft. White piedra is caused by *Trichosporon beigelii*.

eruption. Griseofulvin is not recommended for use in pregnancy. It is ineffective against *Candida* species and pityriasis versicolor. The paediatric dosage is 125 mg three times daily, in an elixir form if necessary, and the adult dose is 0.5–1 g daily. Treatment for 4–6 weeks is sufficient for tinea of the groin, body, scalp and feet. The minimum time required to eradicate the fungus from the hand and fingernails is 5 months. Treatment of tinea pedis and toenails is not so satisfactory, particularly in those with poor peripheral circulation. The drug is required for at least 18 months, and often for 2 years, to eradicate it from the toenails. Even then it cannot be guaranteed that the nails will completely clear. It is now superceded by terbinafine and itraconazole.

- **Itraconazole** This oral triazole is used particularly for nail infections in a pulse form: of 400 mg daily for a week once a month for 3–4 months.
- **Terbinafine (Lamisil)** This allylamine inhibits squalene epoxidase. This prevents the conversion of squalene to 2,3-oxidosqualene and, therefore, inhibits the formation of ergosterol in the fungal cell wall. The intracellular accumulation of squalene is toxic to fungal cells and is fungicidal; this is advantageous over itraconazole, which is fungistatic. Also terbinafine has a lower mean inhibitory concentration. It is not metabolized through the P-450 enzyme system and, therefore, does not have the risk of drug interactions seen with itraconazole. It is not known to be teratogenic but it is excreted in the milk. It does not need to be taken with meals. Paediatric oral granules (or miniature granules sprinkled over food) are very effective in the treatment of tinea capitis. It is probably more effective than itraconazole in toenail infections. It is also active against *Candida* species. Side-effects are uncommon although maculopapular rashes have been described and subacute drug-induced lupus erythematosus.

Scytalidium infections

Scytalidium dimidiatum and *Scytalidium hyalinum* cause an infection of the feet, palms and nails similar clinically to *T. rubrum* infections.

Aetiology

Infections occur in Africans, Asians and Afro-Caribbeans. *S. dimidiatum*, formerly known as *Hendersonula toruloidea*, is a weak pathogen of higher plants in the tropics and produces a grey or grey-black mould. *S. hyalinum* is similar except that it is non-pigmented.

Clinical Features

Symptoms

The infection causes dryness of the palms or soles and nail disorder.

Morphology

Scaling is prominent particularly in the skin creases (Fig. 15.70).

Distribution

Involvement of the palms and soles is characteristic but, unlike *T. rubrum* infections, both palms may be involved. The nails are involved in a similar manner to tinea.

Management

The diagnosis may be suspected if scrapings are positive for fungus on direct microscopy but negative on culture and if there is no response to oral antifungals. The organism is sensitive to cycloheximide and the laboratory must be warned to omit cycloheximide from the culture medium if *S. dimidiatum* and *S. hyalinum* are to be isolated. The infections have proved resistant to standard antifungals.

Piedra

Piedra are hard, dark superficial nodules (black piedra) and soft white or light brown nodules on the hair shaft (white piedra) caused by *Piedraia horta* and *T. beigelii*, respectively.

Aetiology

Black piedra occurs in the humid tropical regions of the Americas and southeast Asia. White piedra is found in South America, Africa, Central and Eastern Europe and Japan. White piedra is caused by *T. beigelii*, although this probably covers a variety of species. Its importance is that it may be sexually transmitted. The carriage rate is increased perianally in some HIV-positive patients and it is now being reported in disseminated infections of the skin in patients who are immunosuppressed. This form of disseminated infection (*trichosporonosis*) is seen in those immunocompromised, especially from chemotherapy-induced neutropenia and treatment with systemic steroids. It has also been described in patients who have prosthetic heart valves, haemochromatosis, organ transplants and in intravenous drug abusers. It is a natural inhabitant of the soil but is

Fig. 15.72 Piedra. Soft white or light brown nodules occur on the hair shaft with *T. beigelii*. (Courtesy of Dr Luis J. Méndez-Tovar.)

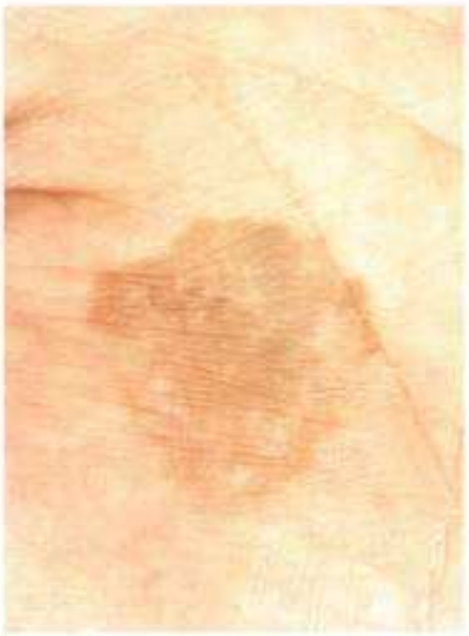


Fig. 15.73 Tinea nigra. A round patch of pigmentation is present on the palm. It is caused by *Hortaea* (*Exophiala*) *werneckii*. (Courtesy of Dr A. C. Pembroke.)

occasionally found in the throat and lower gut flora of hospitalized patients and of 15% of homosexuals, particularly perianally. Trichosporonosis has a poor prognosis.

Clinical Features

Symptoms

Piedra appear as nodules on the hair shaft (Fig. 15.71).

Morphology

The superficial nodules are hard and dark coloured in black piedra and soft and white or light brown in white piedra (Fig. 15.72).

Distribution

Black piedra particularly affects the scalp but the beard, moustache and pubic area may be involved. White piedra is more common in the beard, moustache and genital hair than in the scalp.

Management

The diagnosis can be established by direct microscopy. On culture, black piedra is not inhibited by cycloheximide but white piedra is. Treatment is shaving or cutting the hair. Terbinafine is effective.

Trichosporonosis is usually diagnosed by skin biopsy and culture but the clinical appearances are of scattered necrotic papules and pustules. Lipid-associated amphotericin formulation is given systemically.

Tinea nigra

A superficial fungus infection causing a localized pigmentation on the palms.

Aetiology

It is caused by *Hortaea* (*Exophiala*) *werneckii*. It is rare in the UK but occurs sporadically worldwide.

Clinical Features

Symptoms

Tinea nigra presents as an asymptomatic patch of pigmentation on the palms, after an incubation period of 2 weeks.

Morphology

There is a striking well-defined brown pigmentation (Fig. 15.73).

Distribution

Usually on a palm, occasionally sole, neck or trunk.

Management

Hyphae may be identified in potassium hydroxide preparations and the fungus may be cultured. It responds to Whitfield's ointment or topical thiabendazole.

Infestations of the skin 16

The common infestations that give rise to irritation of the skin are pediculosis, scabies and insect bites. Tropical disorders that may be transmitted by an infected vector, such as leishmaniasis (sandflies), or which result from direct entry by the parasite via the skin (e.g. larva migrans or schistosomiasis) are described in Chapter 17. Lyme disease, conveyed by ticks, is described in Chapter 13.

Scabies

An intensely itchy, contagious eruption caused by an infestation with a mite that burrows into the stratum corneum.

Aetiology

Scabies is an infestation with *Sarcoptes scabiei*, an eight-legged mite or acarus (Fig. 16.1). It is transmitted from one individual to another by prolonged physical, and usually intimate, contact. It cannot be caught from short social contact such as shaking hands. Fomite transmissions from mites attached to clothing, bedding or towels is uncommon, as Mellanby showed during World War II. Only three of a hundred conscientious objectors became infected after spending the night in sleeping bags recently vacated by sufferers with the disease. It is most often contracted by the promiscuous rather than by those with monogamous or celibate habits. However, infants and small children are susceptible because they are handled often and long enough to permit the acarus to travel to their skin from an infected individual. The disease may spread quite easily between children as they have more physical contact than adults, i.e. through play.

Having reached a new host, the acarus searches for a mate. The gravid female then burrows (Fig. 16.2) into those areas of skin where the stratum corneum is thickest, particularly the palms and soles. The female lays eggs at the rate of two a day for about 2 months. The larvae hatch in 2–4 days and leave the burrow. The nymph moults in 4–6 days and the adult commences the cycle again. The female may be ovigerous within 14 days of being an egg.

An immune response to the acarus develops within a few weeks and pruritus and a papular eruption result. Immunoglobulin levels, particularly IgG and IgM, increase.

Clinical Features

Symptoms

The itch begins insidiously on the thighs. It is intermittent but is usually worse after bathing or undressing and in bed. The itch soon intensifies and involves all areas except the face. The condition is contagious and bedfellows or other intimates will become similarly infected.

Morphology and distribution

The finding of a burrow is diagnostic (Fig. 16.3); it is a serpiginous, linear track, a few millimetres long, slightly raised and with a black dot visible at

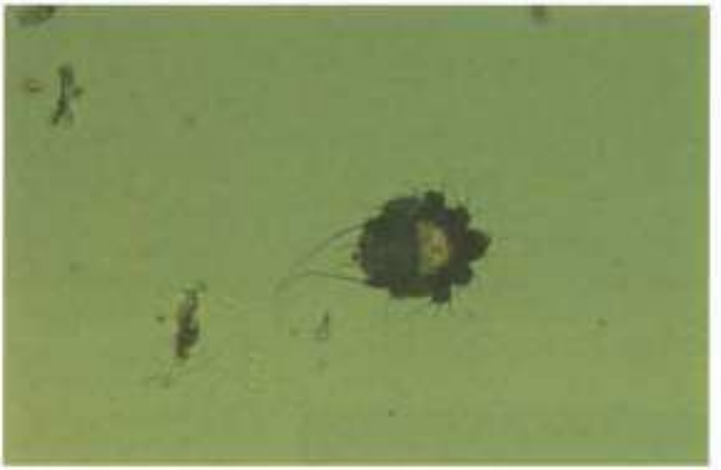


Fig. 16.1 Scabies. Scabies is caused by an acarus or mite, *Sarcoptes scabiei* var. *hominis*. It burrows into the skin but may be extracted with a needle and identified under a light microscope. Dermatologists should be able to do this.

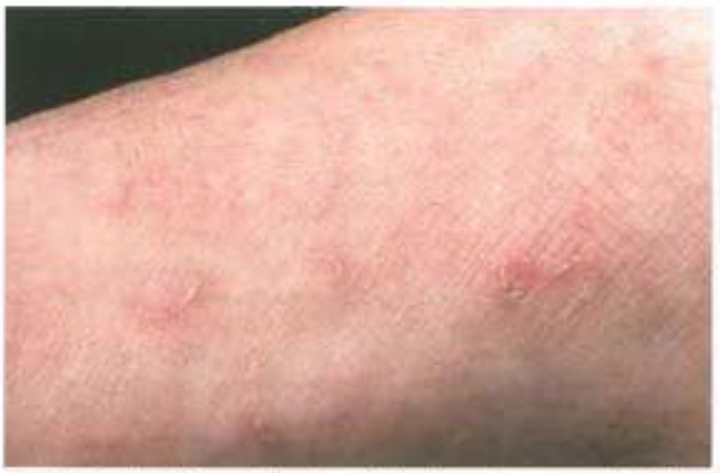


Fig. 16.2 Scabies. It is mandatory to search for burrows in anyone who is itching. They are linear, slightly raised serpiginous lesions, usually found where the stratum corneum is thick.

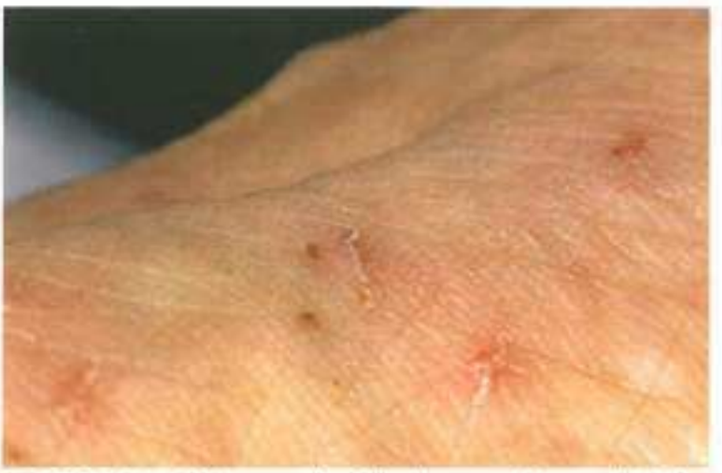


Fig. 16.3 Scabies. This is commonly mistaken for eczema. However, a lack of previous history of eczema and extreme irritation coupled with the finding of burrows such as those illustrated here, confirms the diagnosis.

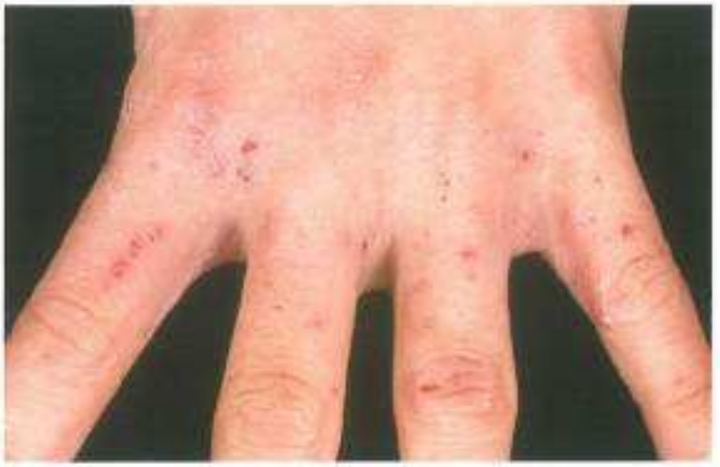


Fig. 16.4 Scabies. Itchy papules and burrows occur between the fingers. Excoriations are seen in addition.

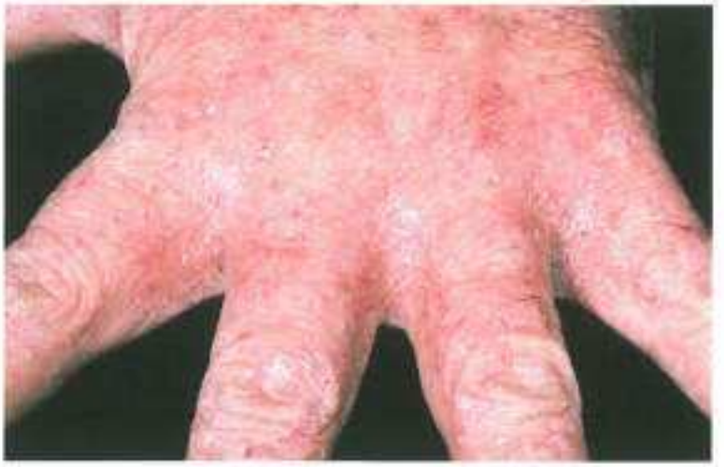


Fig. 16.5 Scabies. It is good medical practice to examine the hands carefully in anyone who is itching. Papules and eczematous changes may be explained by finding a burrow, the habitat of the gravid acarus.

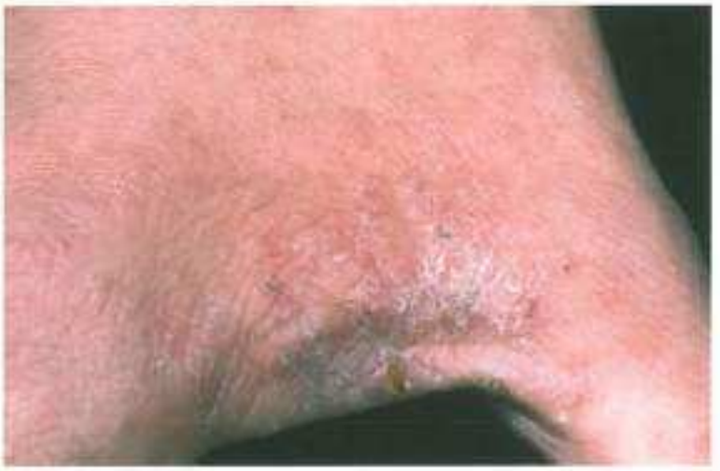


Fig. 16.6 Scabies. The skin over the first dorsal interosseous muscle is usually involved as are the palms and hyper- and hypothenar eminences.

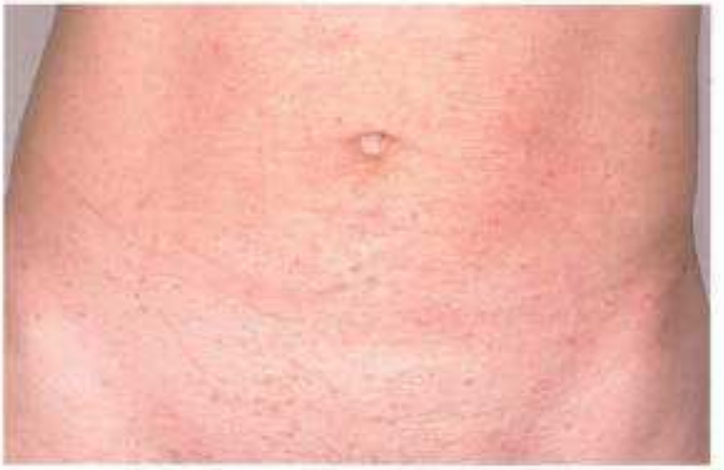


Fig. 16.7 Scabies. A fine papular eruption is visible on the trunk as part of the allergic reaction to the presence of the mite.

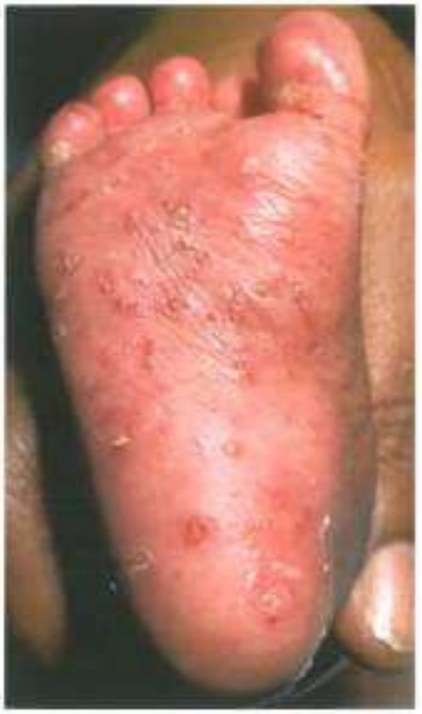


Fig. 16.8 Scabies. Papules and burrows occur on the soles and sides of the feet. Children are particularly affected in this manner. Infants often rub their feet together to relieve the itch.

one end. An observant patient notices that the burrows are particularly pruritic. The characteristic locations are along the sides of and between the fingers (Figs 16.4, 16.5 and 16.6), on the palms and around the wrists.

The burrow is visible early on but symptoms are delayed a few weeks and result from an *allergic reaction* to the mite. An erythematous papular eruption develops on the trunk (Fig. 16.7), which is particularly well visualized by observing the patient from the side in a good light. Papules are also found between the fingers including over the dorsal interossei, on the thenar eminences, elbows, buttocks, fronts of the axillae, around the nipples and on the genitalia. In infants it occurs especially on the soles (Fig. 16.8), and along the sides of the feet and hands (Fig. 16.9). The male genitalia are so frequently involved (Fig. 16.10) that there is an adage that papules or nodules on the penis and scrotum are virtually pathognomonic of scabies in an itching patient. In some, the papules enlarge to become nodules, which may persist for many weeks and remain intermittently itchy despite successful eradication of the infestation. The face and scalp are rarely involved except in infants and in the elderly.

The unpleasant itch leads to *widespread excoriations*, secondary to scratching. *Bruising* is often marked, particularly on the thighs of women. A *patchy eczema* (Fig. 16.11) may occur on the limbs, as a result of scratching, which frequently leads to an erroneous diagnosis and prescription of topical steroids, which are immunosuppressive and, therefore, permit the mites to flourish. However, on direct questioning, most patients will note that topical steroids, although producing momentary relief, make the condition worse.

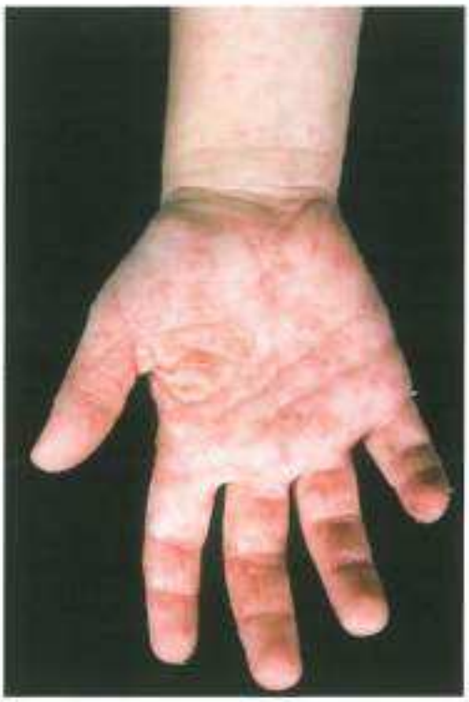


Fig. 16.9 Scabies. The papules are clearly visible on the palms and forearms in this 3-year-old. Closer inspection with the aid of an illuminated magnifying glass should reveal burrows.

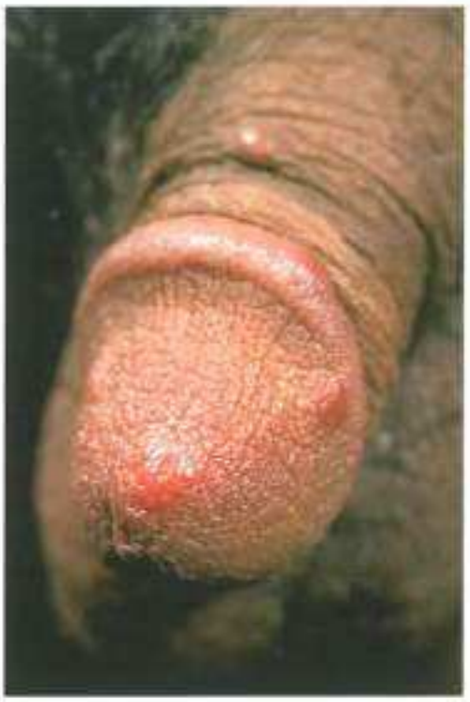


Fig. 16.10 Scabies. Papules on the glans, shaft of the penis and scrotum are virtually pathognomic of scabies.

The physical signs vary greatly between healthy individuals, probably in relation to their personal hygiene. The more frequently the patient bathes, the more likely the acarus is to be removed mechanically, thus reducing the load of infestation but not the degree of itch. In these patients, there will be fewer burrows, which renders the diagnosis a little more difficult. It is wise to consider the possibility of scabies in any person who complains of irritation.

Complications

Norwegian scabies (crusted scabies)

Occasionally, extensive infestations with acari do occur in immunosuppressed patients, including those with acquired immunodeficiency syndrome (AIDS). Institutionalized individuals with Down's syndrome are also prone to this, perhaps because they have disordered immunological functions or possibly because they may not scratch and, therefore, fail to eliminate a certain proportion of the mites mechanically. In recent years, patients who have been misdiagnosed as having eczema have been treated with topical steroids, which are immunosuppressive and so allow easy dissemination of the mites.

The diagnosis of Norwegian scabies is usually made after members of the staff of an institution develop scabies in an epidemic form, as this variety of scabies is highly infectious and, unlike ordinary scabies, requires a minimum of contact for transmission. On examination, a myriad of burrows will be found, particularly on the palms, although the most striking feature is the degree of crusting and scaling of the skin (Fig. 16.12). This may be virtually universal, including the face (crusting on the ears

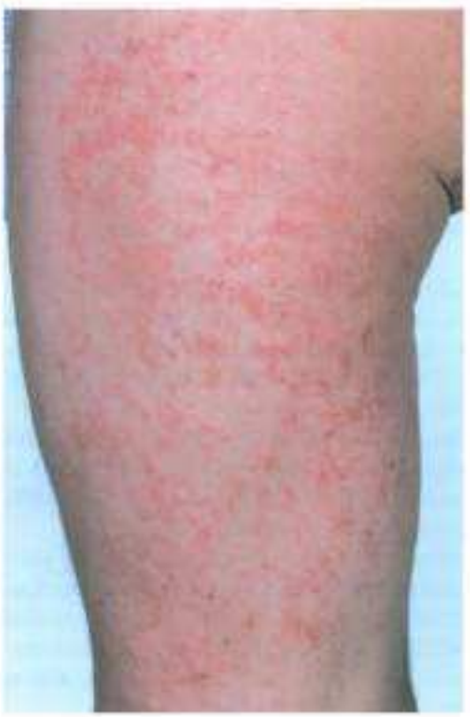


Fig. 16.11 Scabies. Eczema may result from the scratching and particularly from treatment with acaricides, which may cause diagnostic confusion.

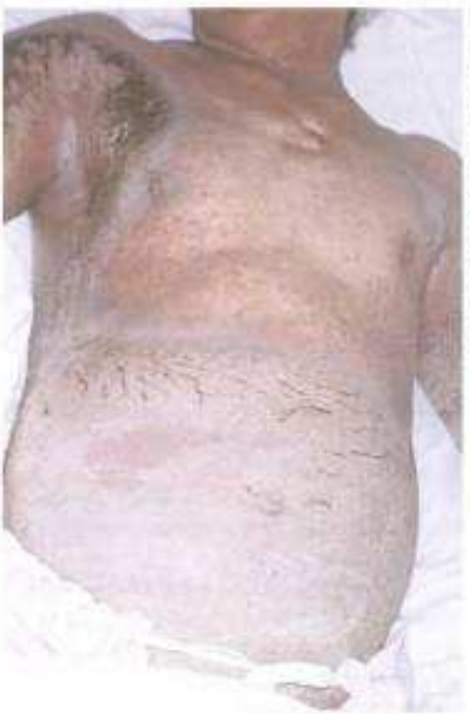


Fig. 16.12 Norwegian scabies. This man was admitted to hospital and treated with powerful topical and systemic steroids for eczema. The correct diagnosis was made when several patients, nurses and doctors developed irritation of the skin and the author was asked to examine them. (Courtesy of St Mary's Hospital.)

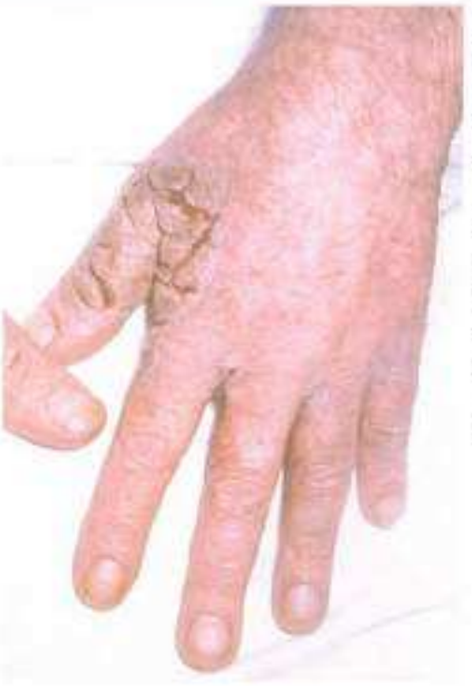


Fig. 16.13 Norwegian scabies. Crusting is present between the finger webs (same patient as Fig. 16.12). The lesions were teeming with acari and were, therefore, highly infectious. The author (then a resident) subsequently contracted the condition after extracting the acarus to prove the diagnosis. The condition responded to routine treatment with gamma benzene hexachloride. (Courtesy of St Mary's Hospital.)

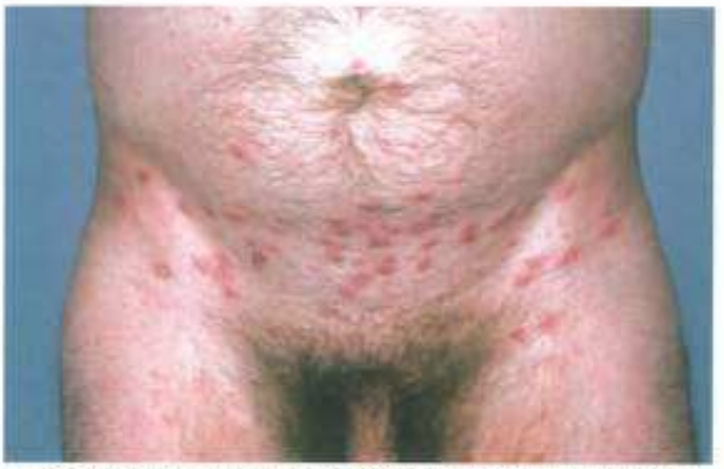


Fig. 16.14 Nodular scabies. The papules may enlarge to form nodules, which may persist for weeks after treatment and remain intensely itchy, particularly in the axillae, hips and groin.

(see Fig. 14.80) is characteristic in AIDS) but will predominate in those areas where the eruption of ordinary scabies is usually found, for example between the fingers (Fig. 16.13).

Nodular scabies

Nodular scabies occurs in a few patients. There are very itchy, firm, red-brown papules and nodules (Fig. 16.14) that occur most commonly on the genitalia, elbows and in the axillae. The nodules persist for many months despite treatment rendering the patient uninfectious. They may be treated with superpotent topical steroids or injected with triamcinolone. They represent an exaggerated hypersensitivity response.

Management

Scabies is eminently treatable but success depends on explanation and follow-up. All topical remedies are potential irritants and may result in secondary dermatitis, so causing confusion. The treatment should be applied after a warm bath to all the skin, excluding the face. It is important to emphasize this because the soles of the feet, between the toes, the natal cleft, the genitalia and under the nails are often forgotten. Clearly the treatment will fail if the mite happens to be present on skin that is not treated and this point should be made to the patient. The lotion is left on the skin for 24 hours, then washed off and reapplied for a further 24 hours.

There are several treatments available.

- **Sulphur (5%) in yellow paraffin** This has been used for centuries and still is in third-world countries. It is effective but may irritate the skin. A 2.5% concentration may be used in infants as an alternative to Lindane.
- **Gamma benzene hexachloride** Lindane was the preferred treatment (Quellada, UK; Kwell, USA) but is now discontinued since a few cases of neurotoxicity have been described in young babies.
- **Benzyl benzoate** Most patients comment that benzyl benzoate (Ascabiol) burns or irritates their skin. It is probably best avoided because postscabetic irritant dermatitis is common.
- **Permethrin 5% cream** Permethrin (Nix, USA) is effective as a single application. It should be washed off after 10 hours. It is poorly absorbed and therefore considered to be safe. It disrupts the function of voltage gated sodium channels of arthropods causing depolarization of nerve cell membranes and thus disrupts neurotransmission.
- **Monosulfiram 25%** This is diluted with two to three parts of water to form an emulsion just prior to application. It is applied daily for 2 or 3 days. An antabuse effect is reported with alcohol ingestion (flushing, sweating and tachycardia). It is not available in the UK.
- **Malathion 0.5% lotion (Prioderm)** This is effective. It should be left on for a day and the treatment repeated 3 days later.
- **Crotamiton (Eurax)** This does have an antiscabetic effect but it is not recommended because it is not as effective as standard treatment.
- **Ivermectin** This is an oral antiparasitic agent that induces paralysis in arthropods and nematodes by interruption of the aminobutyric acid-induced neurotransmission. It is used in onchocerciasis, loaisis, bancroftian filariasis, strongyloidiasis and for larva currens and migrans. It is not licensed for scabies at present but is a useful additional treatment in Norwegian scabies. It is given as a single dose of 150–200 mcg/kg body weight. It is not ovicidal. A second dose is required 1 week later.

Problems of irritant dermatitis arise if further applications are made. However, despite exhortations to the contrary, patients do frequently use the treatment several times, largely because the itch does not subside straight away. Although the disease is cured by two applications, the allergic response may take up to a month to subside. Consequently, although the itch lessens considerably and the patient can at last sleep, spasmodic bouts of itching may occur. The patient mistakes this for further disease and reapplies the lotion.

Scratching in scabies induces a partial eczematous response in some patients and treatment may compound this. It is essential, therefore, to follow up the patient after treatment since a topical steroid and an emollient may be required to settle the secondary eczema. Surprisingly, scratching rarely produces secondary bacterial infection.

The management of scabies in infants and pregnancy has caused concern in recent times, but there does not seem to be any evidence that topical acaricides are harmful in pregnancy and the adverse neurological effects attributed to Lindane in infancy are probably explained by misuse.

Scabies is a contagious disease. It is important to check for other sexually transmitted disorders and imperative to trace and treat contacts. Certainly it is wise to treat the patient's immediate family, whether or not they are symptomatic. If the patient is informed that the disease is usually contracted a few weeks prior to the first symptoms, he or she may be able to recall the original contact and arrange treatment accordingly.

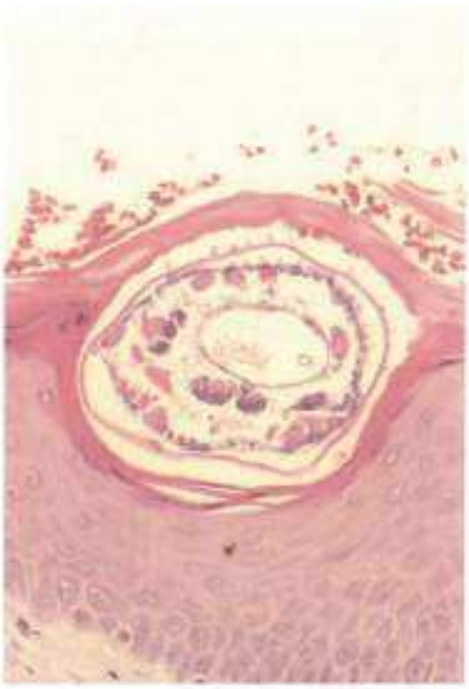


Fig. 16.15 Scabies. The burrow is present within the stratum corneum.

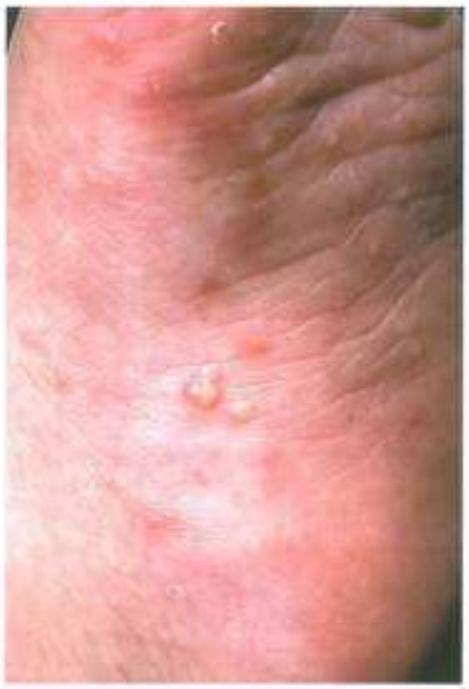


Fig. 16.16 Infantile acropustulosis. Recurrent crops of itchy sterile pustules occur on the soles and palms. They may continue into childhood. The cause is unknown.

Diagnosis

The burrow is the hallmark of scabies. The acarus may be magnified and seen quite readily in the burrow using a dermatoscope. The acarus or her eggs, however, should be extracted by scraping the burrow with a pin, to which the mite conveniently will cling. The acarus is only just visible to the naked eye but can be demonstrated microscopically when placed on a slide with a few drops of potassium hydroxide: this is the ultimate proof of diagnosis. It is often helpful for the patient to see the mite under the microscope, in order to appreciate the diagnosis and its treatment. A biopsy (Fig. 16.15) is seldom necessary but is sometimes helpful in nodular scabies.

The diagnosis of scabies should be entertained in any patient who is itching. The common diseases to be confused with scabies are eczema, lichen planus, insect bites, prurigo and *infantile acropustulosis* (Figs 16.16 and 16.17). The latter is of unknown aetiology and not common. Crops of pustules (which contain neutrophils and occasionally eosinophils) may continue into early childhood. It is harmless and there is no treatment.

Pediculosis

An itchy infestation of the skin with blood-sucking lice.

Aetiology

Lice have six legs and are wingless. There are two species that are specifically ectoparasitic on humans: *Phthirus pubis* (the crab louse) and *Pediculus humanus*. The latter (Fig. 16.18) may affect the head (pediculosis capitis) or body (pediculosis corporis). Both are elongated in shape but have slight anatomical differences. *P. pubis* is shorter, as broad as it is long and does not move far (its name is derived from the crab-like claws on its legs with which it grasps the pubic hair and where it prefers to remain); *P. humanus* is quite mobile. Unlike the acarus, no immunity develops in the human to the louse species, so repeated infestations may occur.

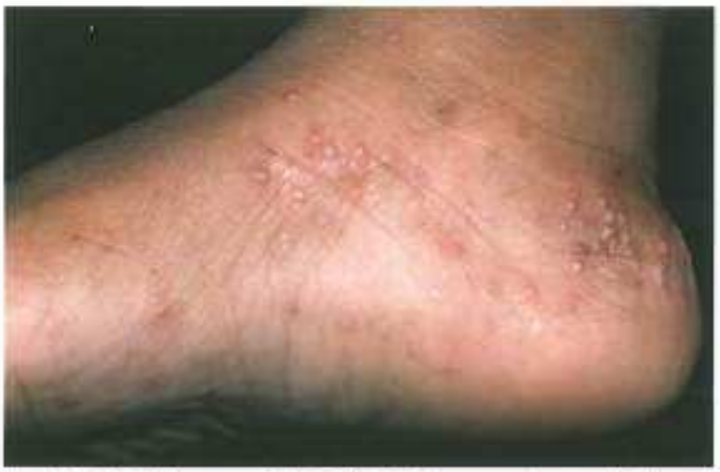


Fig. 16.17 Infantile acropustulosis. This infant has recurrent crops of itchy sterile pustules on the soles and palms. It is not uncommon in Afro-Caribbeans and Afro-Americans.

Fig. 16.18 Pediculosis capitis. A mass of nits and pediculi are present in this man's hair. A louse is clearly visible at the bottom left of the field. (Courtesy of St Bartholomew's Hospital.)

PEDICULOSIS CAPITIS

An infestation of the scalp particularly in schoolchildren and occasionally adults.

Aetiology

It became remarkably common in the 1990s, having been particularly prevalent during World War II and then rare by 1960. Transmission is by shared headgear, hair accessories, blow dryers, bedding, brushes and combs, and the general physical head to head contact between children and their parents and teachers. The lice feed exclusively on blood every 4–6 hours. The female louse lives for a month and lays 5–10 eggs a day.

Clinical Features

Symptoms

The scalp is intensely itchy and the lice are apparent to the naked eye when they move.

Fig. 16.19 Pediculosis capitis. The eggs of the pediculus are attached to the shafts of the hair and cannot easily be dislodged.

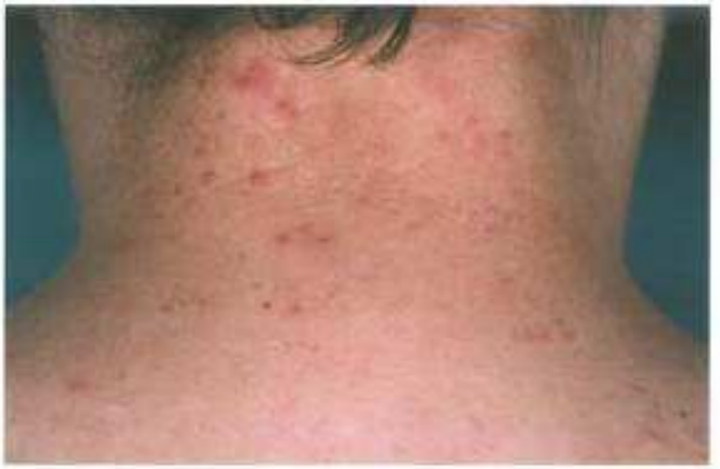


Fig. 16.20 Pediculosis capitis. Urticated papules occur on the back of the neck, and should prompt a search for pediculi and nits in the hair.

Morphology

The eggs (known as 'nits') are attached to the shafts of the hairs, close to the scalp (Fig. 16.19), where its warmth favours hatching. In hot countries, they may be visible further away. The eyelashes may also be affected.

Distribution

The scalp is affected by small itchy grouped papules that occur on the nape of the neck (Fig. 16.20) particularly, but also on the wrists.

The lice do transmit *S. aureus* and *Strep. pyogenes* and if the diagnosis is missed, secondary bacterial infection may supervene, with matting and crusting of the hair and lymphadenopathy. The child may be quite unwell at this stage.

PEDICULOSIS CORPORIS

Aetiology

Pediculosis corporis is a disorder of the unfortunate and is rare in normal circumstances. It occurs under disaster conditions where there is chaos, overcrowding and a breakdown in hygiene. Under these circumstances, the body louse may transmit *Richettsia*, which result in typhus or relapsing fevers and *Bartonella quintana* (a facultative intracellular bacterium), which causes trench fever. Vagrants are frequently affected because they acquire the infestation from other inhabitants and shared bedding in temporary, unsatisfactory accommodation. This louse is not found on the skin, although it sucks blood and feeds off the patient. It lives and breeds in the clothing and bed clothing.

Clinical Features

Symptoms

There is intense pruritus on the body.

Morphology

There are urticated papules, widespread excoriations and sometimes sepsis. As a result of continual scratching, the skin becomes pigmented, thickened, dry and scaly.

Distribution

The lesions of pediculosis corporis occur on areas of the skin closest to the clothes, such as the shoulders, neck, breasts and around the buttocks.

PEDICULOSIS PUBIS

Aetiology

Phthirus pubis (the crab louse, so called because of its crab-like claws; Fig. 16.21) is usually transmitted sexually but may be contracted from borrowed infested clothing, towels and bedding. It occurs in all races, but more rarely in those with less pubic hair. The adult can live for 36 hours away from the host. The eggs are viable for 10 days.

Clinical Features

Symptoms

There is an intense itching in pediculosis pubis.

Morphology

The crab louse and its eggs are readily visible.

Distribution

The infestation occurs primarily in the pubic hair (Figs 16.22 and 16.23), but it may spread, especially in a hirsute individual, to the limbs, chest, axillae and even eyebrows or eyelashes, although rarely the scalp.

Fig. 16.21 *Phthirus pubis*. The crab-like claws are well illustrated in this electronmicrograph. (Courtesy of the Fernbank Science Center.)

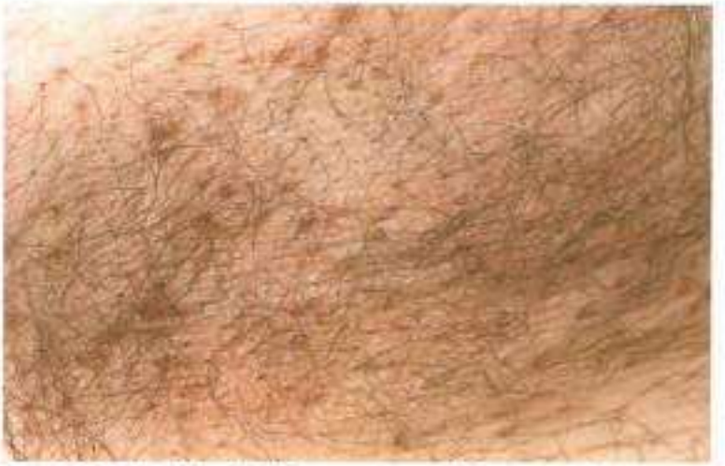


Fig. 16.22 Pediculosis pubis. Brown specks are visible amongst the hairs, which on closer inspection may be identified as crab lice and nits.

Fig. 16.23 Pediculosis pubis. Several crab lice are visible, but sometimes a skilled eye is required to spot them in dense hair and amongst perifollicular erythema. (Courtesy of Dr J. G. Long.)

Fig. 16.24 Nits. The upper egg is white and empty, denoting past infection, but the lower is viable and contains a developing nymph and is brown in colour. (Courtesy of Dr J. G. Long.)

Management of Pediculosis

The diagnosis is normally obvious, for the pediculi may be seen moving and can be picked off with forceps, attached to adhesive tape and visualized microscopically. Affected hairs may be cut off and the oval egg capsule (nit) may be seen attached to the hair shaft under the microscope (Fig. 16.24). Nits may be distinguished from dandruff, hair casts or gels, because they are firmly attached and cannot be slid off the hair shaft.

Body lice may be missed because the physician fails to examine the clothing, particularly the seams of the underclothes. In the hirsute, a skilled eye may be necessary to spot the crab louse amongst perifollicular erythema and excoriations.

Since the lice live off but not on the skin, the patient will recover if separated from the infested clothing and given a fresh set. A mild topical steroid may be required if eczematization has occurred secondary to scratching and systemic antibiotics if there is associated sepsis. A frequent mistake, however, is to apply pediculocides to 'delouse' the patient and then give them back their old infested clothing to wear, which does not benefit them at all.

There are a number of topical treatments for pediculosis capitis and pubis. They should be left on for 12 hours and repeated 10 days later to destroy any lice that may hatch in the interim. Clothing may be disinfected with malathion dusting powder or in a tumble dryer. Topical treatments are as follows:

- **Malathion 0.5% and carbaryl 5%** These are anticholinesterases. Ova and insects are killed within 2 hours. Alcohol-based lotions may sting, smell or irritate (particularly the scrotum) and an aqueous base is preferable.
- **Gamma benzine hexachloride (Lindane)** This is effective, although resistance is being reported. It is banned in some countries because of fears of absorption and neurotoxicity.
- **Phenothrin and permethrin** These pyrethroid compounds are insecticidal neurotoxins, originally derived from dried chrysanthemum flowers. Resistance, however, is occurring.
- **Physical removal** The nits should be removed with a fine-tooth comb.

Systemic therapy

- **Ivermectin** This is used off-label orally 200–250 mcg/kg on days 1 and 8 in resistant cases, including for eyelid nits if they do not respond to being stifled by petrolatum applied twice daily for a fortnight.

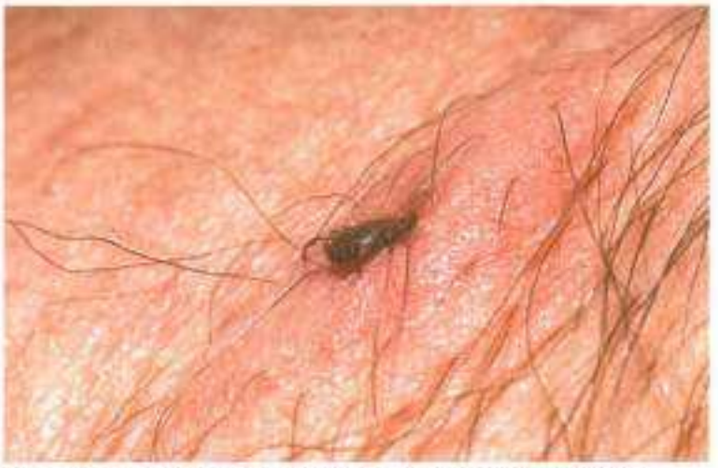


Fig. 16.25 Tick bite. Ticks transmit a number of diseases including Rocky Mountain spotted fever, typhus and Lyme disease.

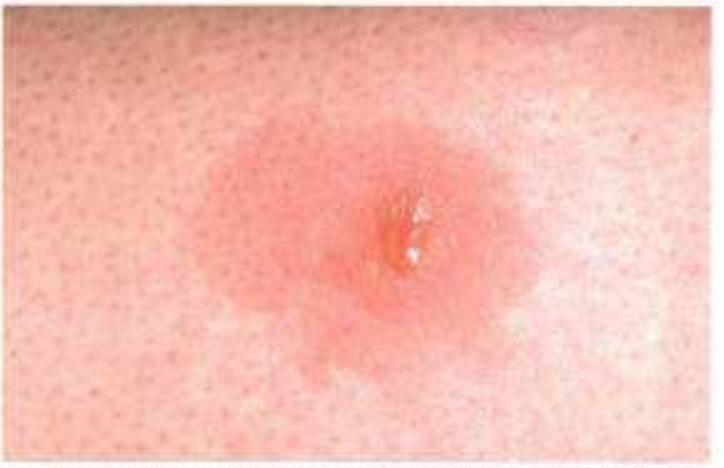


Fig. 16.26 Insect bites. A central vesicle is sometimes visible within an urticarial lesion.

Insect bites

Bites are inflammatory reactions to a biting or stinging arthropod, usually causing itching and sometimes pain. The insect may act as a vector of disease.

Aetiology

The problem occurs worldwide; the causes vary with location and so a knowledge of local arthropod behaviour is essential. There are several common sources.

- **Domestic pets** Dogs and cats carry fleas, sarcoptic mange (animal scabies) and *Cheyletiella* species, another arthropod. It is sometimes difficult to persuade owners that their pet – which 'never goes out' or 'is ever so clean' – is responsible; the offending animal of course may not be the patient's own but that of a friend whose home is visited periodically.
- **Birds** Birds, especially pigeons, may carry mites or fleas, and the house should be examined to see whether there are nests on the window ledges, under the eaves or in the attic. The insects gain entry into the home via open windows.

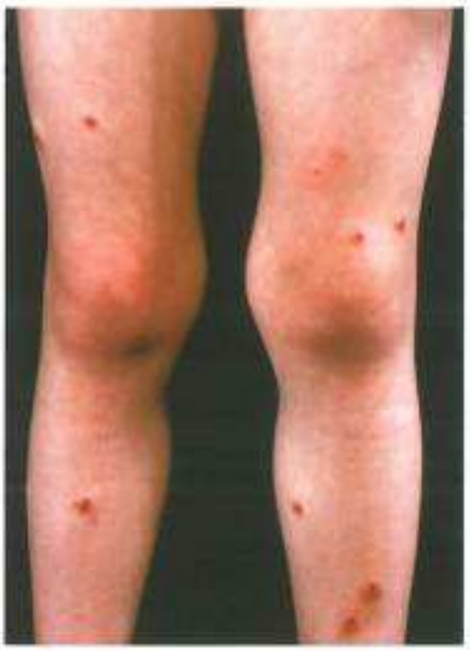


Fig. 16.27 Insect bites. The lower legs are a very common site. Bites are intensely pruritic and, therefore, excoriated. (Courtesy of St John's Hospital for Diseases of the Skin.)

- **Gardens** Foxes and hedgehogs carry fleas. They frequent suburban gardens, and pets may become infested from them. A particular problem in England has been the *brown tail moth caterpillar*, which lives on the leaves of trees and may fall on individuals walking below. Pronounced eruptions occur secondary to the urticating spines of the caterpillar.
- **Bedding, furniture and soft furnishings** Bed bugs (*Cimex lectularius*) live in crevices in furniture and walls.
- **Travel** Travel abroad may result in exposure to mosquitoes, ticks (Fig. 16.25) and sandflies. These may transmit diseases, for example malaria (mosquitoes), Rocky Mountain spotted fever (ticks) and leishmaniasis (sandflies). Sea urchins and jellyfish may be encountered while swimming in warmer waters. Larva migrans (an infestation with dog and cat hookworms) can be acquired on the beaches of the Caribbean, southeastern USA and Thailand.

Vectors

Some transmit disease. There may be more than one vector for the same disease, e.g. flies and ticks both carry tularemia. Different vectors may alter the pathogenesis so that *Bartonella* causes cat scratch disease or bacillary angiomatosis and the louse causes endocarditis.

Fleas are at their most prolific during the summer and early autumn. The cat flea (*Ctenocephalides felis*) is the usual source. Flea collars are not effective deterrents. Fleas breed in cracks, crevices, floorboards and soft furnishings, especially if they are dusty and dirty. Fleas are well suited to centrally heated houses and fitted carpets. They can survive for months without a meal and will attack new occupants of a dwelling that has lain empty, so it is important to discover whether the previous occupant had kept pets. Fleas are vectors for endemic typhus, bubonic plague, brucellosis, melioidosis and erysipeloid.

Clinical Features

Symptoms

The cardinal symptom is itch. The patient may have initially suspected bites but then discounted the possibility, as often only one member of the household is affected. This relates to the individual's immune response (more common in atopics) rather than to the bite itself. This can mislead patient and doctor.

Morphology

There is a wide spectrum of clinical presentations, including anaphylaxis for hymenoptera, but in the main, lesions may consist of urticarial wheals, sometimes with a central vesicle (Fig. 16.26) and often excoriated (Fig.

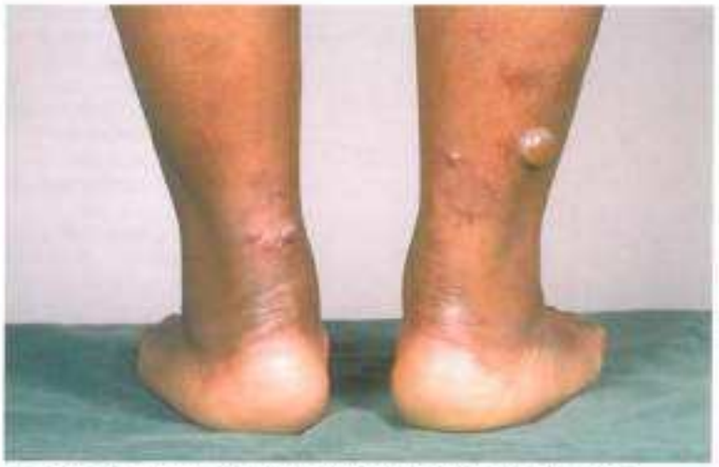


Fig. 16.28 Insect bites. Urticarial papular, bullous and postinflammatory pigmented lesions are present in this West Indian child. Flea bites are most common in the summer and autumn.

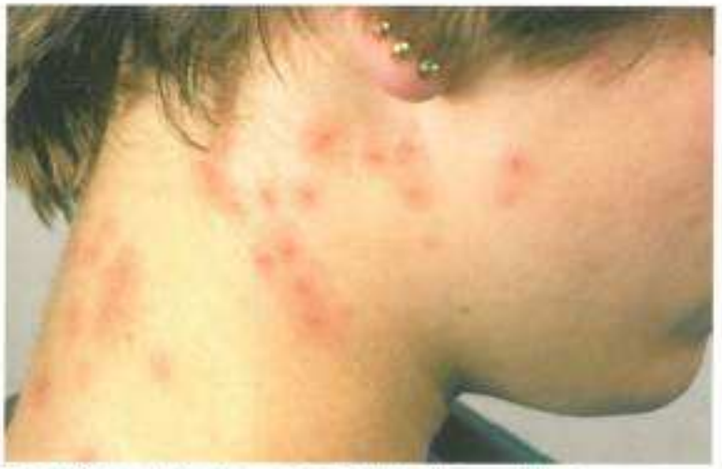


Fig. 16.29 Insect bites. Large urticarial wheals with a central punctum are present on the neck and face. They are grouped in linear arrangements.

16.27). Papules and vesicles, and occasionally large blisters, may be present, and postinflammatory pigmentation can occur. There is often secondary bacterial sepsis, especially in warm climates.

Distribution

The lesions are usually scattered asymmetrically over the body or concentrated primarily on the lower legs and ankles (Fig. 16.28).

Fleas often produce a group of three or four lesions in a linear arrangement, often referred to as 'breakfast, lunch, tea and dinner' (Fig. 16.29). They particularly attack the lower limbs and especially the ankles. Women and children are more prone than adult males because trousers are usually preventative.

Cheyletiella are mites that colonize cats, dogs, rabbits, foxes, squirrels and some birds. Puppies are most commonly affected; they are asymptomatic: the animal develops fine scaling rather like dandruff along the midline of the back, sometimes with loss of hair. The mites can penetrate clothing to attack humans and cause urticarial or papulovesicular eruptions. The distribution usually corresponds to where the animal is held in contact with the human; lesions are, therefore, found on the lap (lower chest, abdomen, forearms and thighs). The human condition is more common in the autumn and winter than in the summer (when the animals are out of the house more often).

Animals may acquire scabies (sarcoptic mange) and pass it on to humans. Dogs are particularly affected and they suffer from severe pruritus with scaling and loss of hair over the face, ears and elbows. In humans, there is no incubation period for animal scabies nor are burrows found, unlike human scabies. The eruption is immensely itchy and multiple tiny red papules appear on parts of the body in contact with the animal, particularly the trunk and limbs.

Caterpillars are the worm-like larval forms of Lepidoptera (moths and butterflies). They develop irritating hairs, sharp spines and various toxins as a defence against predators. They usually result in urticarial wheals on exposed areas (Fig. 16.30). Thus the brown tail moth caterpillar (Fig. 16.31) lives on the leaves of trees and may fall on individuals walking below. Others cause localized stings, which may be painful with vesiculation (e.g. saddleback caterpillars in the Southern USA).

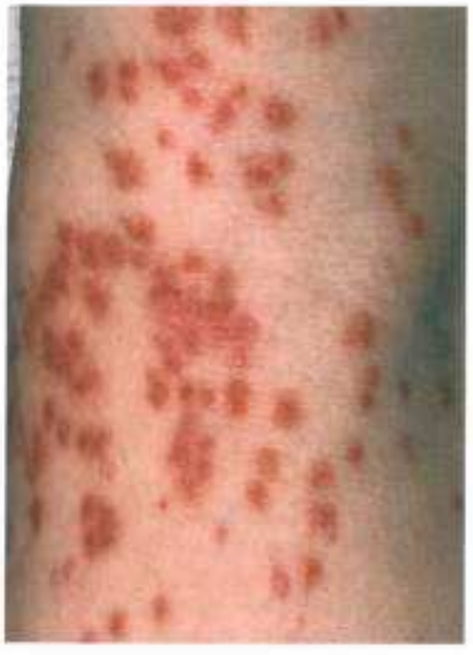


Fig. 16.30 Brown tail caterpillar moth. It has urticating hairs, which produce pronounced wheals on human skin if it fortuitously falls onto it from leaves of trees it feeds on.

Fig. 16.31 Brown tail caterpillar moth. Pronounced urticarial eruptions occur secondary to punctures by the urticating spines of the caterpillar.

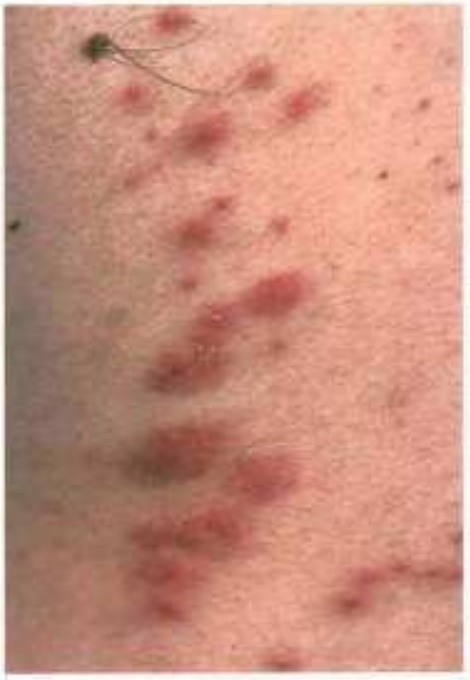


Fig. 16.32 Bed bugs. They produce more inflammation than flea bites, and are quite substantial, red and oedematous. They feed at night on exposed areas of the skin.

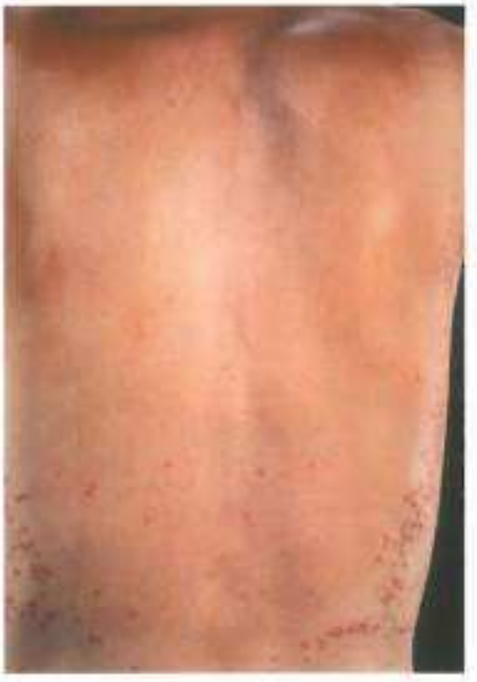


Fig. 16.33 Sea-bather's eruption. A striking urticarial eruption occurs due to entrapment of larvae from a Coelenterate under the wetsuit or swimming costume. Systemic steroids may be required to treat it. (Courtesy of Dr Ruth MacSween.)

Bed bugs (*Cimex lectularius*) produce more inflammation in humans than do fleas. They are wingless, blood-sucking arthropods 7 mm in length. They shun the light and come out at night to feed on exposed areas of skin that are not covered by night attire or bedding. Initially, the symptoms take a few days to appear, but latterly only a few hours. The lesions may be quite substantial, red and oedematous (Fig. 16.32), and blood may be found on the bed clothing the following morning, though most patients sleep on unaware of the attack. With recurrent attacks, the patient may become quite unwell, with secondary sepsis, fever and lymphadenopathy. The bugs favour substandard dwellings with cracked woodwork, loose skirting boards and peeling wallpaper. They are the vectors for American trypanosomiasis (Chagas disease).

Jellyfish, anenomes and corals (Cnidaria, Coelenterata) are marine invertebrates; they have tentacles that contain stinging cells (nematocysts) which release a venom from a thread-like structure. They cause linear collections of localized small wheals, which may be haemorrhagic or vesicular and even ulcerate on occasion at the site of contact with tentacles.

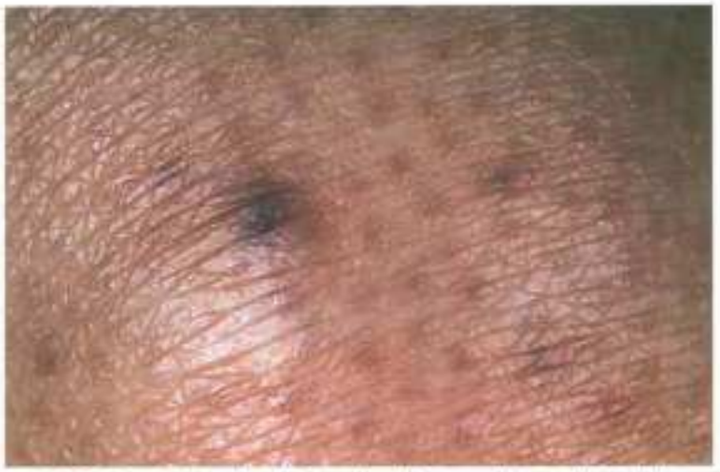


Fig. 16.34 Sea urchin spines. If spines from the sea urchin are retained in the skin (here of the knee), a granulomatous response results.

A striking urticarial eruption, *sea-bather's eruption*, has been described that occurs under a swimming costume; it is caused by the entrapment of larvae from a coelenterate from which the nematocysts are discharged and produce the skin eruption (Fig. 16.33).

Swimmer's itch (syn. *cercarial dermatitis*) is an immunological reaction to the free swimming cercarial stage of non-human schistosomiasis occurring 2 days after exposure to sporocysts (motile cercariae) released from freshwater or aquatic snails into warm water in the summer months. These reinfect their definitive hosts (waterfowl or mammals) and live in the blood vessels of intestinal walls and are excreted as ova in their faeces into water, where they hatch into ciliated larvae, which in turn infect snails (their intermediate hosts). It is a self-limiting pruritic urticated eruption occurring on exposed sites (as opposed to under the costume in sea-bather's eruption). Efforts have been made to disinfect lakes by feeding treated corn to infected waterfowl.

Sea urchins have pedicellariae between their spines; when the urchin is stepped upon, these produce an immediate and intense burning pain with local oedema, which subsequently heals. If some of the spines are retained at the sites of penetration, a delayed granulomatous response occurs (Fig. 16.34).

Ticks have six legs as larvae and eight as adults and are the second most important vectors of disease after mosquitoes through their salivary secretions. These include Rocky Mountain spotted fever (*Dermacentor* ticks), Q fever, Ehrlichiosis (*amblyomma*, lone star ticks), tularemia and African tick bite fever. Ticks need to be attached for 24–48 hours for transmission of disease. All stages (larva, nymph and adult) except eggs can transmit. *Ixodes* cause Lyme disease. Commercial tick removal tools are better than forceps.

Management

The diagnosis can sometimes be difficult to prove. One is often faced with a disbelieving patient, so some investigation is required. The following measures may be useful.

- **The 'SOS' appointment** It is useful to examine the patient when the eruption is at its height, when the tell-tale urticated papules may be present. It is also easier for patients to recall exactly where they have been and what they have been doing in the preceeding 48 hours, which may give a clue to the source of infestation.

- **Examination of the pets** Red-brown collections of the faeces from the fleas may be found on the animal's coat, or loss of hair and profuse scaling from *Cheyletiella* infestation. Specimens may be collected by standing the animal on a piece of brown paper (shiny side up) and brushing it vigorously. Scurf, hair and scale may then be collected and sent to an entomologist for microscopic examination.
- **Examination of the house** The patient should examine every room, window sill and eave for specks that may represent the parasite or its parts, and these should be brought for examination. If the patient has a pet, the pet's bedding and favourite armchair and other haunts should be particularly examined. (It is useful to vacuum the carpet where the animal sleeps and empty the contents and shake its bedding into a polythene bag. The contents can be examined by an entomologist.) In difficult cases it is helpful to call in the Public Health Department.
- **Biopsy** Insect bites produce a specific pathology, which consists of a diffuse dermal infiltrate of lymphocytes, plasma cells and often prominent numbers of eosinophils.

Clearly the source must be identified and treated or the condition will persist. There are several helpful topical remedies.

- **Crotamiton/hydrocortisone (Eurax HC)** Crotamiton is antiparasitic and hydrocortisone is helpful for its anti-inflammatory effect.
- **Calamine** Calamine lotion is antipruritic.
- **Systemic antihistamines** These are useful especially at night.
- **Systemic antibiotics** These are indicated if sepsis is present.

Occasionally the patient is convinced that infestation is present, and yet there is nothing wrong on examination. Specimens are brought along but may consist only of dust and scales of the skin. This is *delusional parasitophobia* (Ch. 29).

A complication of any insect bite is *papular urticaria*. This affects small children predominantly and consists of recurrent attacks each year. Most lesions are the result of fresh bites, but some authorities believe that a specific hypersensitivity occurs that leads to urticated lesions not necessarily preceded by a bite.

- **Pest control** Infested surfaces should be scrubbed clean. Powerful vacuum cleaners will dislodge the eggs. Broad-spectrum insecticides such as chlorinated hydrocarbons are most effective.
- **Prevention** Insects are most active at dawn or dusk and avoidance of these hours is sensible. DEET (N,N-diethyl-3-methylbenzamide) is the most effective broad-spectrum insecticide and can be used topically. Picaridin and Permethrin (which can be used to treat clothing) are effective against mosquitoes and ticks. Garlic and citronella are also useful.

Tropical infections of the skin | 17

A brief account is given here of those tropical disorders that may have a significant cutaneous component. These include the mycobacterial infections of leprosy, the sandfly transmitted protozoan disease of leishmaniasis, disorders caused by worms, including trematodes (schistosomiasis) and nematodes (dracunculosis, filariasis, loiasis, onchocerciasis and larva migrans), and fungal infections. The last include the subcutaneous implantation of fungi (sporotrichosis, mycetoma and chromoblastomycosis), the systemic mycoses of the endemic primary respiratory types (histoplasmosis, blastomycosis and coccidioidomycosis), the opportunistic infections of aspergillosis, trichosporosis and fusaria, and cryptococcosis, which may be an opportunist or endemic. Their full description and management properly belong to works on tropical diseases; however, with the rapidity of modern travel they may present to a general practitioner or dermatologist.

Leprosy

A chronic granulomatous infection principally of the skin and nervous system caused by *Mycobacterium leprae*.

Aetiology

Although Hansen described the causative acid-fast bacillus in 1873, leprosy was still believed for many years to be a familial disorder and its stigma remains formidable. The incubation period is probably 2–5 years. It is usually acquired in childhood from a multibacillary parent. Conjugal infections account for less than 5%. Leprosy is a disorder of tropical countries, particularly India, Africa, southeast Asia and South America, transmitted by inhalation or ingestion of infected nasal droplets. The organism invades the Schwann cells that surround the cutaneous nerves. The degree of involvement depends on the immunological status of the patient, the bacteriological load and socioeconomic conditions. Leprosy was classified by Ridley and Jopling into tuberculoid, borderline and lepromatous based on the immunological status of the patient. These types and their intermediates are known as TT, BB, LL, BT and BL. They are determined on the basis of the clinical signs, histopathology, bacteriological index and the lepromin test (Fig. 17.1), a reaction to an intradermal injection of a standard extract of leprosy tissue, which is positive in tuberculoid and negative in lepromatous leprosy.

In paucibacillary leprosy (indeterminate tuberculoid and borderline), there are five or less skin lesions and negative smears. In multibacillary disease (borderline lepromatous and lepromatous), there are six or more lesions and positive smears. In the field where slit skin smears are not available, leprosy is classified by the number of skin lesions, but this is not very accurate.

The incidence is falling because of multidrug therapy as recommended by the World Health Organization (WHO). In lepromatous leprosy, there is a defective cell-mediated immune response with resultant bacillary multiplication through many tissues. The skin lesions are symmetrical and extensive, in contrast to those of tuberculoid leprosy. Neurological involvement occurs latterly, probably because the immunological response to the presence of the bacilli in the nervous tissue is minor. The disease is highly infectious from nasal discharges, unlike tuberculoid leprosy, which is not infectious at all. The anergy is specific in that patients can mount a delayed hypersensitivity reaction to *Mycobacterium tuberculosis*. The disease spreads in lepromatous leprosy via the blood to cool, superficial areas such as the eyes, upper respiratory tract, testes, and to the small muscles and bones of the hands, feet and face. The skin is extensively involved. In tuberculoid leprosy, the other polar form, cell-mediated immunity is strong, bacilli are not readily found and the infection is restricted to a few skin sites and to the peripheral nerves.

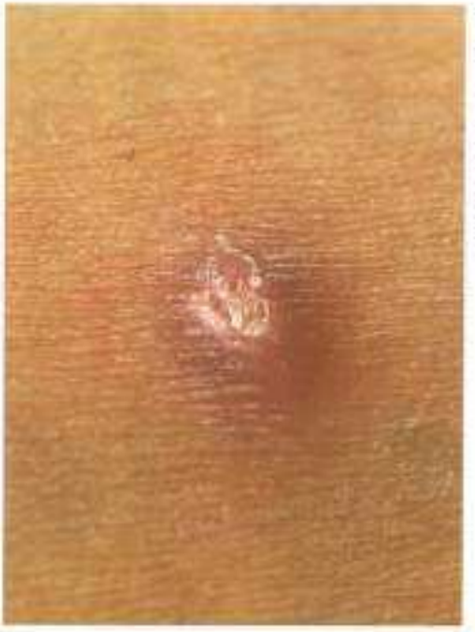


Fig. 17.1 Mitsuda (lepromin) test. This is a reaction to an intradermal injection of a standard extract of leprosy tissue. It is positive in tuberculoid leprosy but negative in lepromatous leprosy. (Courtesy of the Institute of Dermatology.)

Lepra reactions are important tissue-damaging immunological complications that occur in borderline patients who are immunologically unstable. Increased cell mediated immunity ('upgrading') leads to inflammation of skin and nerves and decreased (downgrading) to lepromatous leprosy. Type 1 (reversible) comprises delayed hypersensitivity reactions in response to *M. leprae* antigens in skin (acute inflammation, oedema and sometimes ulceration) and nerves (acute neuritis with impaired, often permanent, nerve damage). They often occur at the start of MDT or during the puerperium. They may be recurrent. Type 2 reactions are the result of immune complex deposition and give rise to *erythema nodosum leprosum*, particularly in borderline patients and in patients with lepromatous leprosy, who have a large bacterial (antigen) load and produce antibodies.

The complications of nerve damage are critical to leprosy. They may occur in the skin lesions themselves as a result of damage to the small dermal sensory and autonomic nerve fibres, causing local sensory loss and decreased sweating. As a result, insignificant and repeated trauma will result in tissue necrosis, which ends in ulceration of the skin with secondary cellulitis and ultimately osteomyelitis, loss of tissue and deformity. Peripheral nerves are particularly vulnerable in superficial situations as they pass through fibro-osseous tunnels; the small increase in nerve diameter caused by infection results in neural compression and ischaemia, leading to regional sensory loss and dysfunction of muscles.

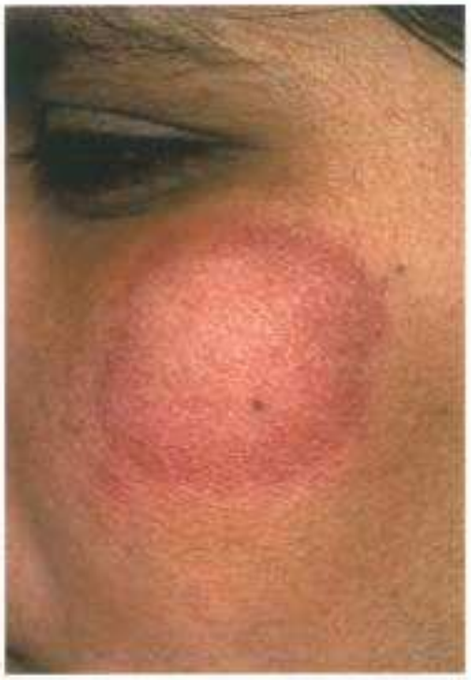


Fig. 17.2 Tuberculoid leprosy. There is a dry, annular, anaesthetic patch on the cheek. Skin biopsy established the diagnosis. (Courtesy of the Institute of Dermatology.)

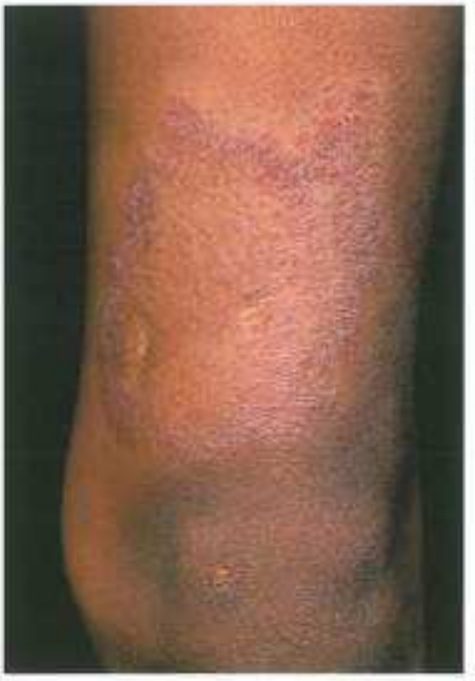


Fig. 17.3 Tuberculoid leprosy. Annular, dry, slightly scaly patches are characteristic. The extensor surface of the knee is a common site. (Courtesy of the Institute of Dermatology.)

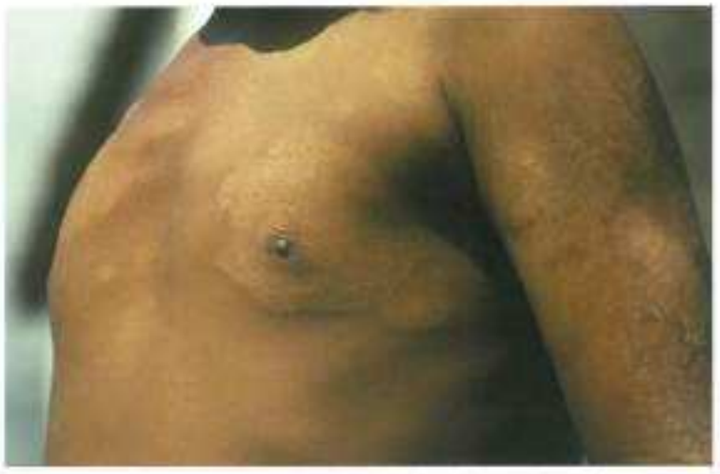


Fig. 17.4 Tuberculoid leprosy. Annular, anaesthetic, hypopigmented patches occur.

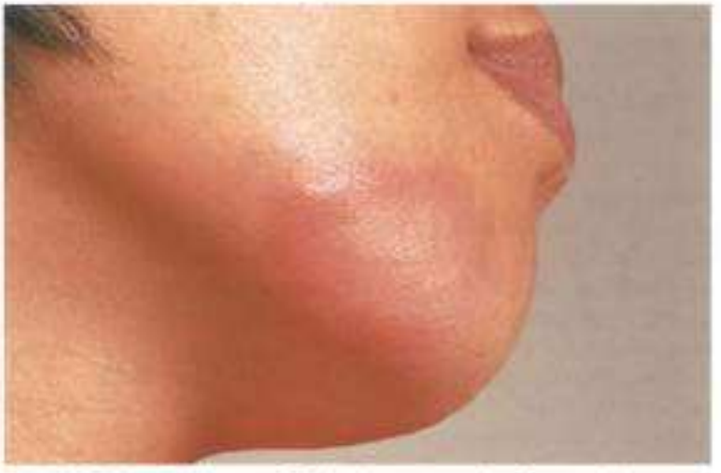


Fig. 17.5 Tuberculoid leprosy. The jaw is a common site. The margin is oedematous. The adjacent nerve was thickened. She had been raised in the Philippines. (Courtesy of St Mary's Hospital.)

HIV does not increase susceptibility to *M. lepnae* or alter the course of the disease, but latent leprosy may be unmasked during immune reconstitution with antiretroviral treatment.

Clinical Features

Tuberculoid leprosy

Symptoms

Anaesthetic skin lesions with subsequent sensory and motor neuropathy.

Morphology

Solitary or few asymmetrically distributed, well-defined red patches occur, often annular in shape with central hypopigmentation (Fig. 17.2). The surface is dry, scaly, does not sweat and is anaesthetic (Figs 17.3 and 17.4).

Distribution

The cool, peripheral parts of the body are affected, such as the buttocks, elbows and knees, extensor surfaces of the limbs and the face (Fig. 17.5).

General medical features

Sensory (numbness) changes are the earliest, followed by granulomatous inflammation of the peripheral nerves, particularly the great auricular, ulnar, median, radial and peroneal. These nerves are thickened and, therefore, palpable and can often be felt entering the lesion and become entrapped within fibro-osseous sheaths. Involvement leads to a peripheral neuropathy with sensory changes, resulting in ulceration of the digits and motor changes with palsies such as footdrop or ulnar nerve paralysis.

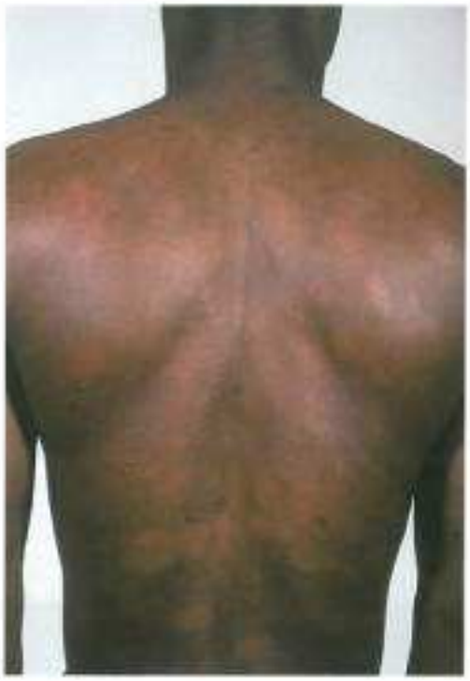


Fig. 17.6 Lepromatous leprosy.
Multiple, symmetrical, hypopigmented macules of varying shapes and sizes are present in this African. A high clinical index of suspicion will result in a diagnostic biopsy.

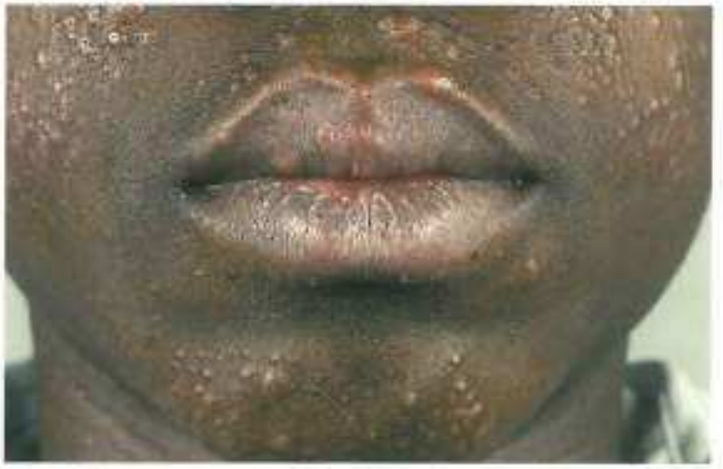


Fig. 17.7 Lepromatous leprosy. Extensive papules and nodules are present in this African. The lips are also involved.

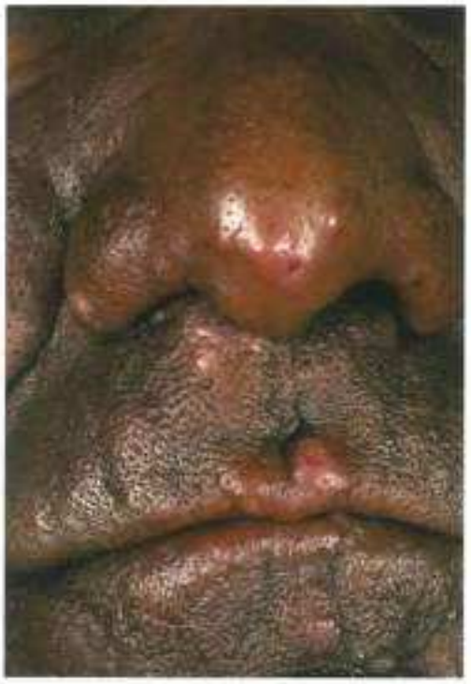


Fig. 17.8 Lepromatous leprosy. The nose and lips are characteristic sites.

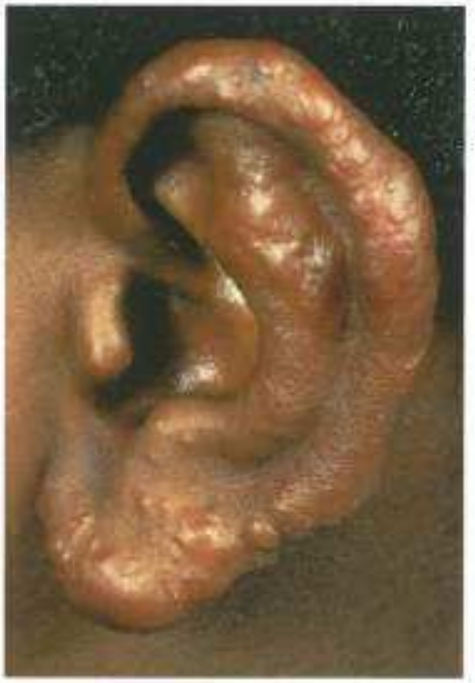


Fig. 17.9 Lepromatous leprosy. Papules and nodules occur around the ears. Leprosy favours the peripheral cooler areas of the skin.

Borderline leprosy

This disorder is a mixture of both tuberculoid and lepromatous leprosy. It is, however, immunologically unstable and can downgrade to lepromatous leprosy or can reverse to tuberculoid leprosy. Neurological signs are often present and annular skin lesions are characteristic. Type 1 reactions are common.

Lepromatous leprosy

Symptoms

The first are usually nasal (stuffiness, discharge and epistaxis). The early cutaneous changes are subtle.

Morphology

Multiple, symmetrical, small, red or slightly hypopigmented macules occur initially; these subsequently become extensive (Fig. 17.6). They have vague and ill-defined borders. Papules (Fig. 17.7), plaques and nodules (lepromata) develop later.

Distribution

The face, arms, legs and buttocks are most common. The cooler areas of the face, such as the lips (Fig. 17.8), nose and earlobes (Figs 17.9 and

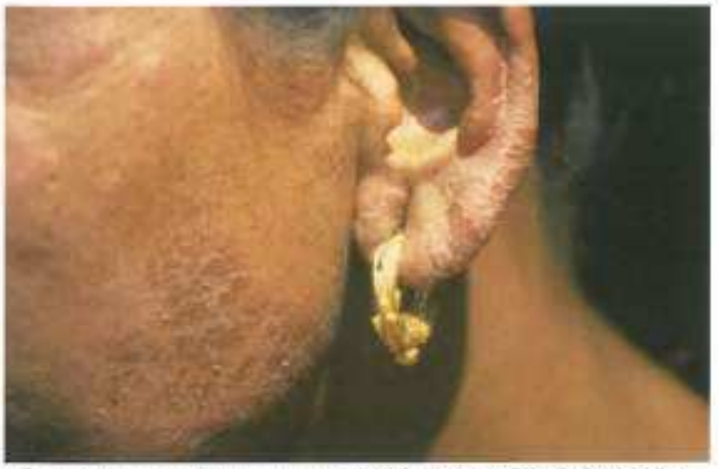


Fig. 17.10 Lepromatous leprosy. There is a diffuse, pink, scaling infiltration on the cheeks and ears.

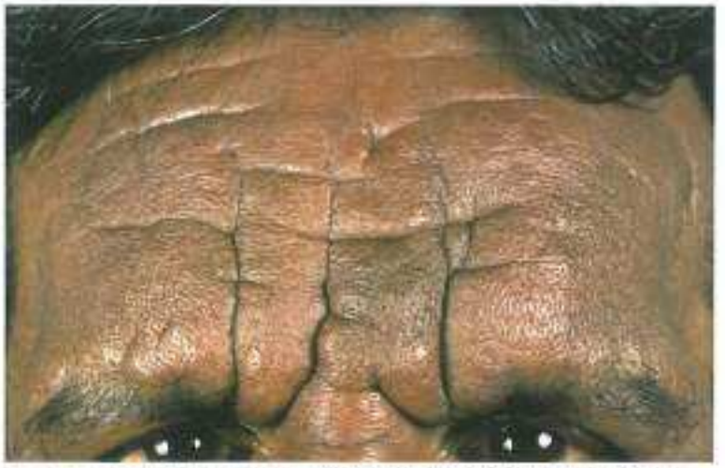


Fig. 17.11 Lepromatous leprosy. Involvement of the forehead has produced deep fissuring, an appearance known as the 'leonine facies'.

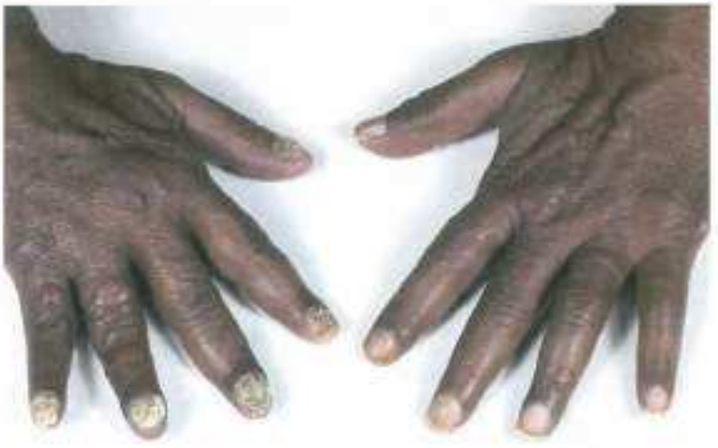


Fig. 17.12 Lepromatous leprosy. Two lepromata are present on the fourth and fifth fingers of his right hand. There is small-muscle wasting from peripheral neuropathy and lines of the right fingernails (from immunosuppression).

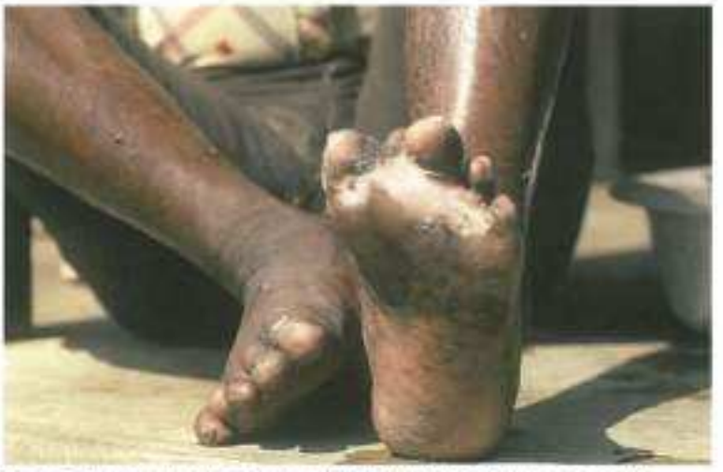


Fig. 17.13 Lepromatous leprosy. Destruction of the digits from repeated unappreciated trauma is an end result of polyneuritis causing glove and stocking anaesthesia.

17.10) are particularly affected. Warm sites such as the axillae and groin are not. Diffuse infiltration of the skin of the forehead causes a leonine appearance (Fig. 17.11) and the eyebrows and eyelashes disappear.

Systemic features

The nose, eyes, testes and bone become involved. Swelling of the ankles and lower legs is common. Glove and stocking anaesthesia develops from polyneuritis (Fig. 17.12), and results in destruction and shortening of the digits from repeated unappreciated trauma (Fig. 17.13) and sepsis. Osteomyelitis is common. Autonomic nervous system involvement results in reduced sweating and hypohidrosis of the hands and feet. The course of the disease is punctuated by frequent febrile exacerbations and erythema nodosum leprosum is a characteristic feature. Blindness occurs in 3% from lagophthalmos (inability to close the eyes), due to damage to the zygomatic and temporal branches of the VIIth nerve leading to exposure keratopathy and of the ophthalmic branch of the trigeminal (Vth) nerve to corneal ulceration, trauma (from rubbing of the eye) and infection. The untreated patient ultimately succumbs from renal failure, amyloidosis or concomitant tuberculosis.

Management of Leprosy

Skin biopsy is helpful. In tuberculoid leprosy, non-caseating granulomas are present but bacilli are conspicuously few or absent (Fig. 17.14). In lepromatous leprosy a large number of acid-fast bacilli (Fig. 17.15) are demonstrable in the diffuse infiltrate of foamy histiocytes (Fig. 17.16) seen histopathologically. They are called 'lepra' cells. The diagnosis can also be made by making a superficial slit into involved skin, smearing the tissue onto a slide and staining for acid-fast bacilli. The bacillary index is a logarithmic scale, which quantifies the density of *M. leprae* on slit skin smears. It is a useful means to assess response to treatment.

Following the recognition that dapsone, in use since World War II, was resulting in resistance when used as monotherapy, the WHO proposed a multidrug approach using dapsone, rifampicin and clofazimine as first-line drugs, particularly in multibacillary leprosy (positive slit skin diagnosis greater than 15 lesions and widespread nerve damage), for 2 years and follow-up for 5 years. The monthly dose of rifampicin (600 mg) and clofazimine (300 mg) is supervised and clofazimine 50 mg and dapsone 100 mg are taken daily. In paucibacillary leprosy, rifampicin and dapsone are given for 6 months and the patient is followed for 2 years or alternatively

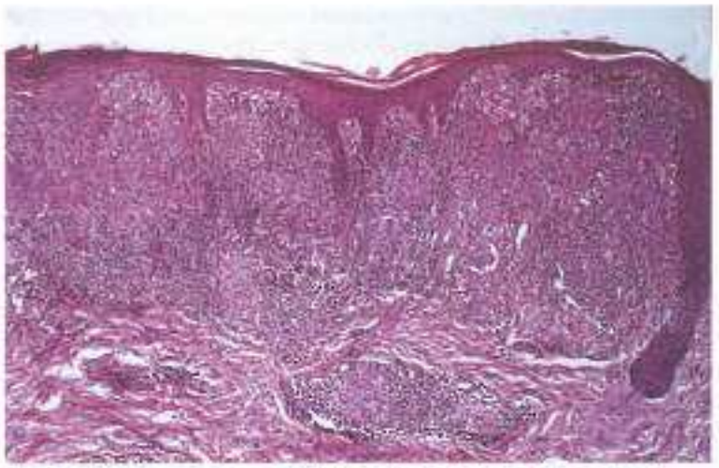


Fig. 17.14 Tuberculoid leprosy. Granulomas are eroding into the epidermis. No acid-fast bacilli are seen on Wade–Fite staining. (Courtesy of Dr S. Lucas.)

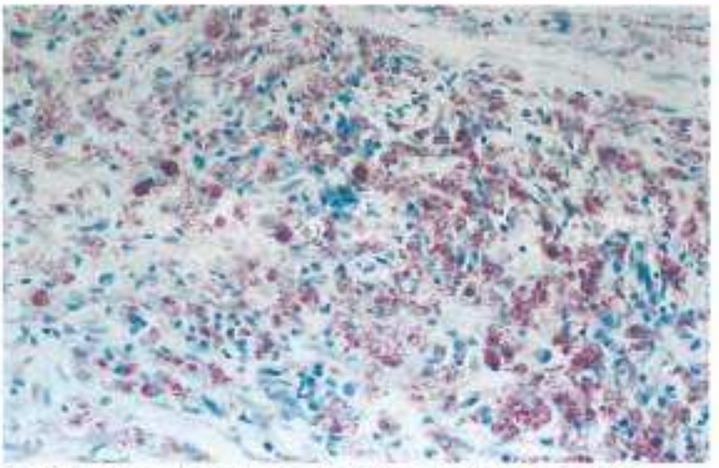


Fig. 17.15 Lepromatous leprosy. Innumerable red-staining bacilli may be demonstrated. The larger intracellular aggregates are sometimes known as globi (Wade–Fite stain).

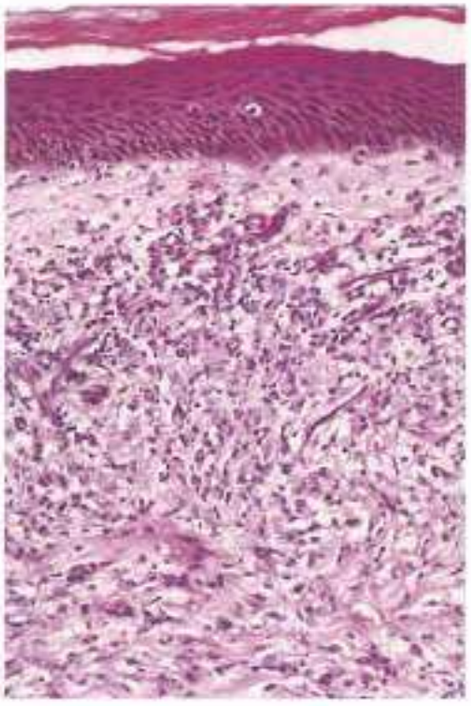


Fig. 17.16 Lepromatous leprosy. A diffuse infiltrate of foamy histiocytes (lepra cells) is separated from the epidermis by a Grenz zone of sparing. There are relatively few lymphocytes.

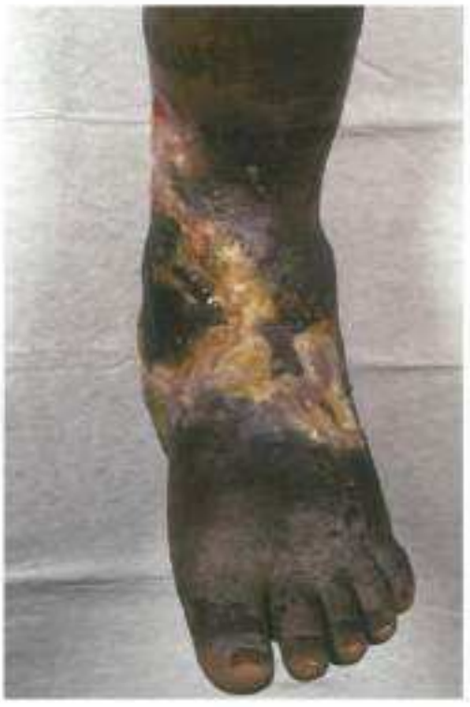


Fig. 17.17 Buruli ulcer. Children most commonly acquire this infection on the legs from contact with contaminated grasses. Extensive ulceration has occurred here and a large eschar is present. The condition is caused by *Mycobacterium ulcerans*. The infection must be widely excised and grafted.

rifampicin, ofloxacin and minocycline are given. Rifampicin causes orange-red coloration of body fluids and clofazamine causes conjunctival discoloration, red-brown or purple skin discoloration, darkening of involved skin and a characteristic ichthyosis of the shins and forearms.

Rifampicin is bactericidal for *M. leprae* but dapsone is only weakly so. Other drugs that are bactericidal for *M. leprae* are being evaluated and these include minocycline, clarithromycin and fluoroquinolones. Severe type 1 reactions usually require prednisolone. Erythema nodosum leprosum may be treated with steroids but thalidomide and clofazimine are important alternatives.

Buruli ulcer

An ulcerative condition of the skin caused by *Mycobacterium ulcerans*.

Aetiology

M. ulcerans is the next most common mycobacterial infection of the immunocompetent after leprosy and tuberculosis. It is a slow-growing acid-fast bacillus, which is harboured by snails, fish, aquatic insects and plants in spiky grass wetlands of tropical and subtropical regions. Endemic in Buruli, a swampland in Uganda especially in the rainy season, it is now a re-emerging global disease of the tropics and subtropics. First cultured in Bairnsdale, Australia at a temperature of 30–32°C when an incubator broke down, it produces a diffusible macrolide toxin with cytotoxic properties called mycolactone. It prevents phagocytosis of live organisms and may delay the development of an inflammatory response and apoptosis. It is easily inoculated into the bare skin of a passer-by, usually a child (Fig.17.17) or adult female.

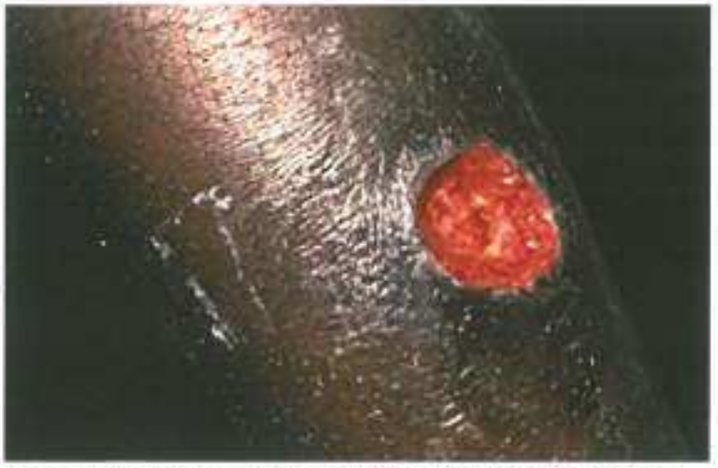


Fig. 17.18 Tropical ulcer. There is a very painful, well defined ulcer of the leg, occurring in malnourished barefoot labourers, possibly due to trauma. This patient lived in Papua New Guinea (Courtesy of Prof. Rod Hay.)

Clinical Features

Symptoms

An ulcer follows trauma.

Morphology

A painless mobile subcutaneous nodule, which becomes fluctuant and ulcerates after a few weeks with deep undermined edges and a necrotic base, measuring many centimetres in diameter.

Distribution

The ulcers usually occur on the legs.

Management

Diagnosis is made by PCR or culture of the organism from a skin biopsy. It grows at 24–31°C. The ulcer needs to be widely excised and grafted as early as possible with rifampicin and streptomycin cover. Untreated cases may be complicated by squamous cell carcinoma.

The differential diagnosis is from *tropical ulcer*, which however is painful. It is a disorder of the malnourished, rural labourers who walk unshod and is probably initiated by trauma. It is most common below the knee, especially around the ankle. It is a well-defined punched-out ulcer (Fig. 17.18), which if neglected may become chronic and destructive, leading to osteomyelitis. *B. fusiformis*, anaerobes and spirochaetes have all been isolated, but there is no uniform agreement on an infective responsible organism. Secondary infection with *S. aureus* and streptococci is common. Early treatment with cleansing and antibodies may prevent later necessity for debridement, grafting and even amputation.

Leishmaniasis

Traditionally, there are three major forms – restricted to the skin (Old World leishmaniasis), mucocutaneous (New World) and visceral. Systemic infection of the mononuclear phagocytic system is known as kala-azar and is caused by *L. donovani* or, in children, *L. infantum*. Cutaneous leishmaniasis is localized purely to the skin and caused by *L. tropica* or *L. major*, and in Ethiopia and Kenya, by *L. aethiopica*. In the New World, *L. braziliensis* and *L. mexicana* produce sores that are often more destructive than their Old World counterparts and may spread to the mucosa, particularly of the nose (American mucocutaneous leishmaniasis).

Leishmania sp. are obligate intracellular parasites and are protozoa that exist in two forms, leishmanial and flagellate. The former occur as small spherical bodies, known as Leishman–Donovan bodies or amastigotes within macrophages. They do not have flagella. The flagellate form is found in the sandfly or on artificial culture media and is known as a leptomonad or promastigote; it is elongated and motile with an anterior flagellum.

Leishmania sp. are transmitted to humans by bites, usually at night, from sandflies (*Phlebotomus* in the Old World and *Lutzomyia* in the New), which are often infected from a rodent or dog reservoir. In the Old World, the organisms are found in crevices in banks, trees, houses and in the burrows of rodents. In the New World, they are found particularly in forests or buildings at the level of tree canopies. They are ingested in the leishmanial form and lodge in the intestine of the insect, where they become flagellate, multiply and migrate to the oral larynx. They are released into human skin following a bite. The parasite enters into the human macrophages and reticuloendothelial system and adopts the leishmanial form.

Susceptibility to infection and delayed resolution is proportional to impaired Th1 immunity. IL-2, IFN-γ, IL-12 (which stimulates NK cells to produce IFN-γ) and TNF-α are important for control of the infection. Drugs which inhibit TNF-α may reactivate previous infection. Survival from kala-azar confers lifelong immunity. The others only give immunity to the individual species.

SYSTEMIC LEISHMANIASIS

Systemic leishmaniasis is viscerotropic and is caused by *L. donovani* and, in children, by a close relative *L. infantum*.

Aetiology

The word kala-azar means the black sickness and refers to the hyperpigmentation of the skin, which may be marked. It is prevalent in India, China, Indo-China, the Mediterranean littoral and some parts of West Africa. *L. donovani* parasitizes the reticuloendothelial cells in the liver, spleen, bone marrow, lymph nodes, lungs and skin. The incubation period is between 1 and 6 months. Children are particularly susceptible in the Mediterranean variety (*L. infantum*), where dogs are reservoirs of infection around the home. Those who have HIV are also vulnerable. In Brazil and East Africa, older children acquire the infection and foxes are the animal reservoir. In India, however, it is a human infection and epidemics occur every decade.

Clinical Features

Symptoms

The patient is feverish, weak, fatigued, anorexic and loses weight.

Morphology

May be specific (papules, nodules or ulcers) or non-specific with increased pigmentation and hair loss.

Distribution

It occurs particularly on the face (around the cheeks, temples and mouth), hands and abdomen. The hair is dry and tends to fall out.

Systemic features

There is hepatomegaly, anaemia, leucopenia, oedema, lymphadenopathy and gross splenomegaly. If untreated, the patient may ultimately succumb.

In some patients after treatment, a condition known as *post-kala-azar dermal leishmaniasis* may occur. Erythematous plaques or nodules involve the face (Figs 17.19 and 17.20) and subsequently the trunk. The lesions may also be hyperpigmented initially, becoming hypopigmented and are often confused with leprosy.

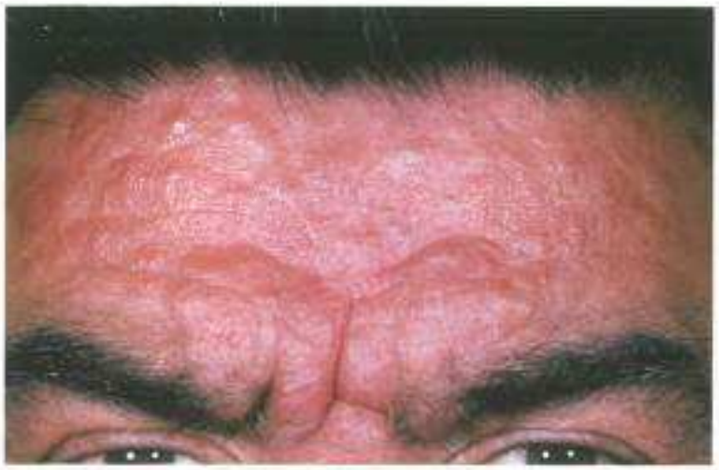


Fig. 17.19 Post-kala-azar dermal leishmaniasis. Erythematous nodules particularly involve the forehead, simulating leprosy, but the eyebrows and ears were spared, which would be unusual for lepromatous leprosy. Biopsy provided the correct diagnosis. (Courtesy of Dr Dowling Munro.)

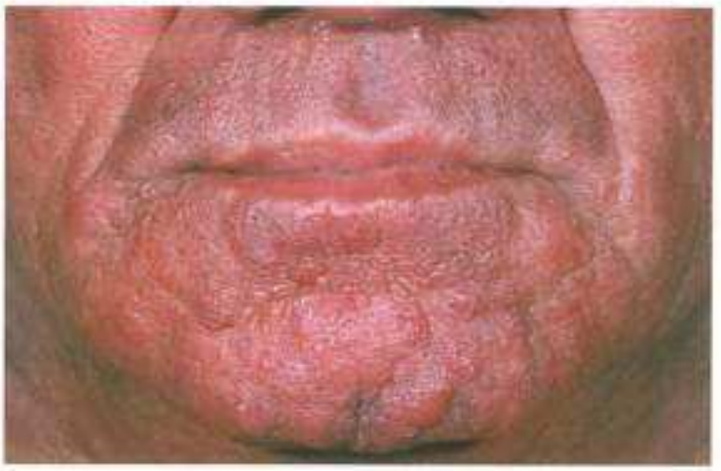


Fig. 17.20 Post-kala-azar dermal leishmaniasis. The erythematous nodules are striking. The condition follows treatment of systemic leishmaniasis in some patients. (Courtesy of Dr Dowling Munro.)

CUTANEOUS LEISHMANIASIS

A granulomatous infection of the skin transmitted by sandflies infected with *L. tropica*, *L. major*, *L. aethiopica* or *L. infantum*.

Aetiology

Cutaneous leishmaniasis is most common in the Middle East (*Baghdad boil*) but also occurs in the Indian subcontinent (*Oriental sore*), China, the countries that made up the Soviet Union and countries around the Mediterranean (Sicily, South of France, Gozo, Northern Spain, Turkey and Israel). There are various forms. *L. major* is contracted from a rodent reservoir, particularly the gerbil in rural areas. It heals within 6 months. *L. tropica* is found in dry urban areas, spreads from person to person and takes up to 2 years to heal spontaneously. The incubation period for these variants may be as short as a few weeks or as long as a year. *L. aethiopica* is found in Kenya and Ethiopia and is different from the preceding types in that its infections last very much longer, the lesions may not crust or ulcerate and the infection is more infiltrative. It may involve the mucosa if the nose or lip is the original site of the bite. In the anergic immunosuppressed patient it can become quite diffuse although without systemic involvement. *L. infantum* causes visceral leishmaniasis in infants but in adults produces a self-healing Oriental sore.

Clinical Features

Symptoms

A spot or sore occurs on an exposed area of skin which may itch.

Morphology

There are a variety of clinical manifestations of cutaneous leishmaniasis.

- **An acute localized process on an exposed part** This is the most common form; it begins as a papule (Fig. 17.21), which may be one or several (Fig. 17.22) which gradually enlarges, becoming a nodule that is

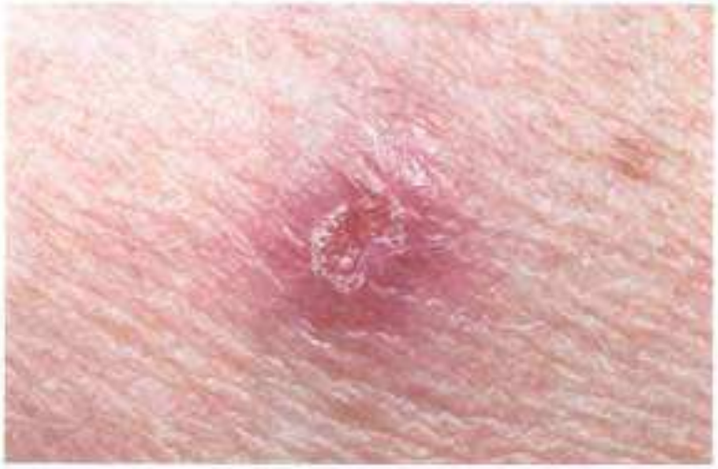


Fig. 17.21 Cutaneous leishmaniasis. The initial lesion is an indurated papule or nodule, which is crusted on the surface before it ulcerates. Biopsy establishes the diagnosis.

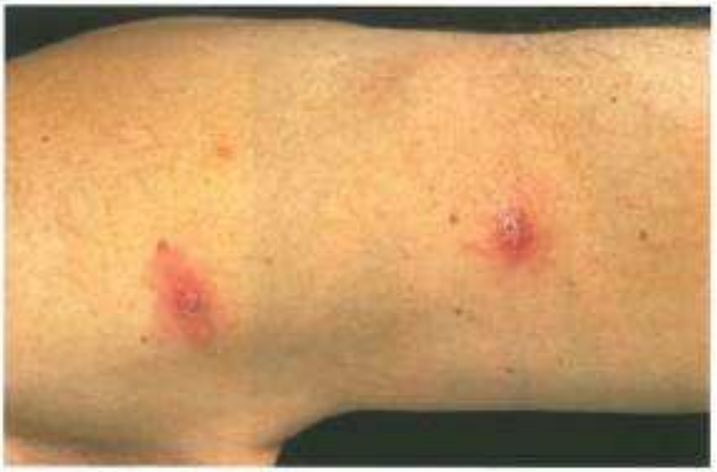


Fig. 17.22 Cutaneous leishmaniasis. Red nodules with a central crusted area are present. This man was bitten by sandflies while working in the desert.

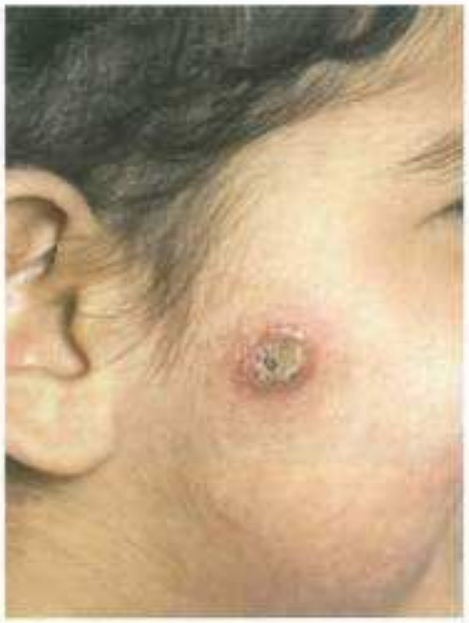


Fig. 17.23 Cutaneous leishmaniasis. This is the acute type of leishmaniasis (sometimes known as Baghdad boil or Oriental sore). This little boy was bitten on the face by an infected sandfly.

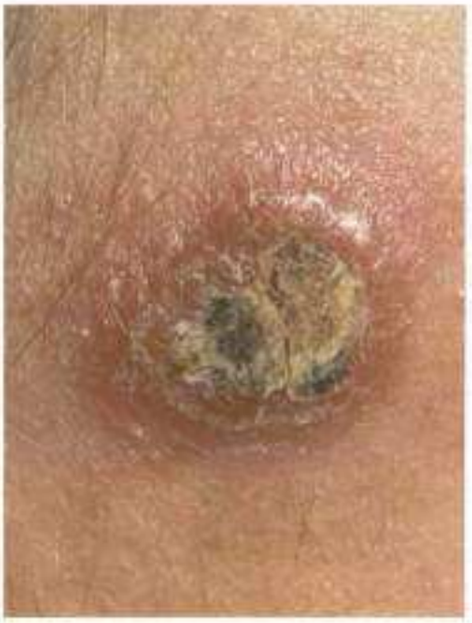


Fig. 17.24 Cutaneous leishmaniasis. The close-up shows a crusted ulcer with an indurated margin.

firm and indurated (Figs 17.23 and 17.24). It is a dark red colour. It develops a crust on its surface and subsequently a shallow ulcer underneath (Fig. 17.25). The verrucous crust may be considerable (Fig. 17.26). The lesion slowly heals centrally leaving behind a scar. Lesions occur particularly along the course of lymphatics in the *L. major* type. Secondary lesions are less common with *L. tropica*.

- **The central facial region** *L. aethiopica* particularly affects this area; there may be a single nodule initially but subsequently satellite papules occur around it. Crusting and ulceration is not so much a feature. The lesions are more granulomatous and infiltrative. They may take several years to heal and often involve the mucosa if the nose or lip was the original site of the bite.
- **Leishmaniasis recidivans or chronic lupoid leishmaniasis** After resolution, there is complete immunity but occasionally there may be a recurrence of brown-red papules close to the scar of the previous cutaneous lesion. It may form concentric rings (Figs 17.27 and 17.28) or ulcerate. The papules coalesce forming a plaque resembling lupus vulgaris (Fig. 17.29). It is persistent and spreads despite good cell-mediated immunity.
- **A generalized variety known as diffuse cutaneous leishmaniasis** This form (Fig. 17.30) occurs in the Sudan, Ethiopia and Kenya and is caused by *L. aethiopica* and in the Americas by the *Mexicana* complex (especially *L. amazonensis*). There is a superabundance of parasites and the initial lesion spreads, forming nodules that do not ulcerate. There is no invasion of internal organs but the condition is slowly progressive and treatment only produces a limited improvement with a tendency for relapse. Those affected have a depressed immunological response and, in particular, a negative response to delayed hypersensitivity tests similar to that which occurs in lepromatous leprosy.

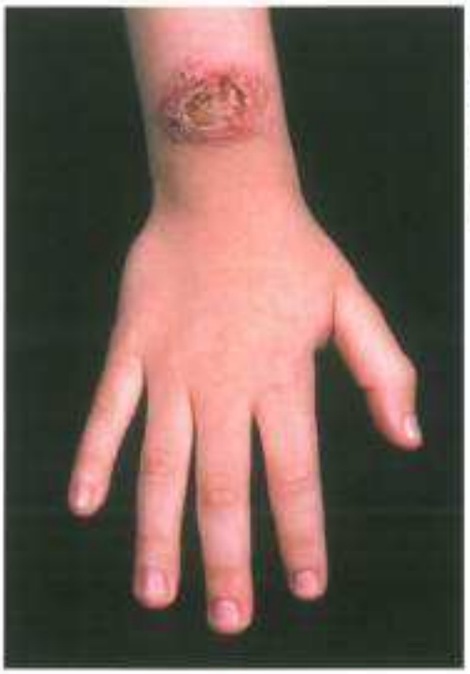


Fig. 17.25 Cutaneous leishmaniasis. Exposed parts of the skin are most at risk from sandfly bites. This 6-year-old has an indurated dark red plaque with a characteristic shallow crusted ulcer centrally.

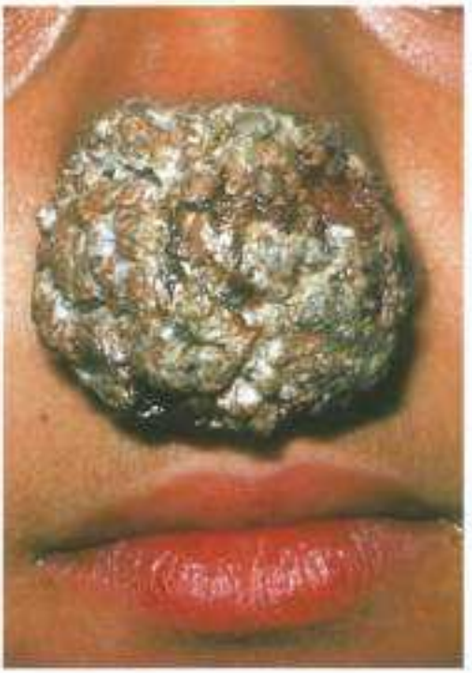


Fig. 17.26 Cutaneous leishmaniasis. There is considerable crusting involving the nose. This may result from either the urban or rural form. (Courtesy of the Institute of Dermatology.)

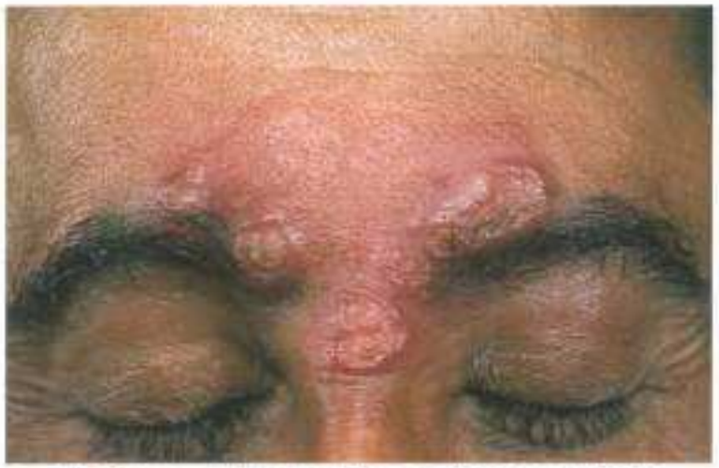


Fig. 17.27 Cutaneous leishmaniasis. There may be one or several lesions. These are beginning to heal. (Courtesy of the Institute of Dermatology.)

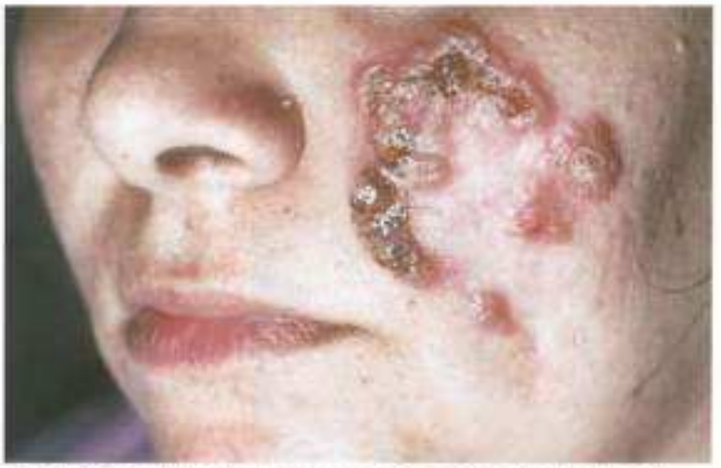


Fig. 17.28 Chronic localized cutaneous leishmaniasis. There are several annular plaques with oedematous margins on the face. (Courtesy of the Institute of Dermatology.)

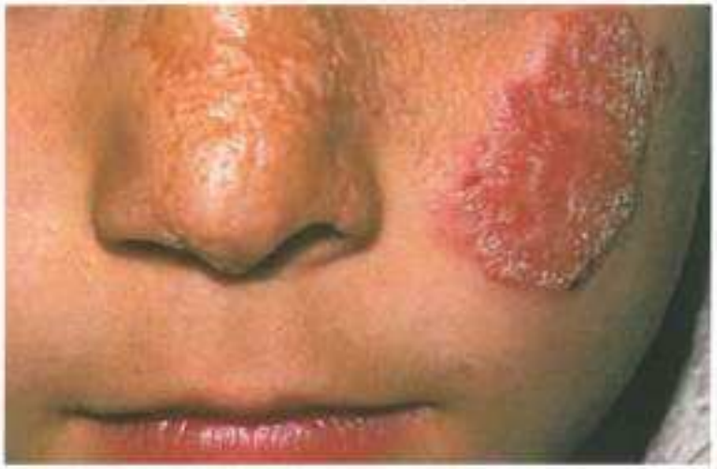


Fig. 17.29 Lupoid leishmaniasis. There may be recrudescence of the disease forming granulomatous plaques, which resemble lupus vulgaris as in this 8-year-old child. (Courtesy of Dr Barbara Leppard.)

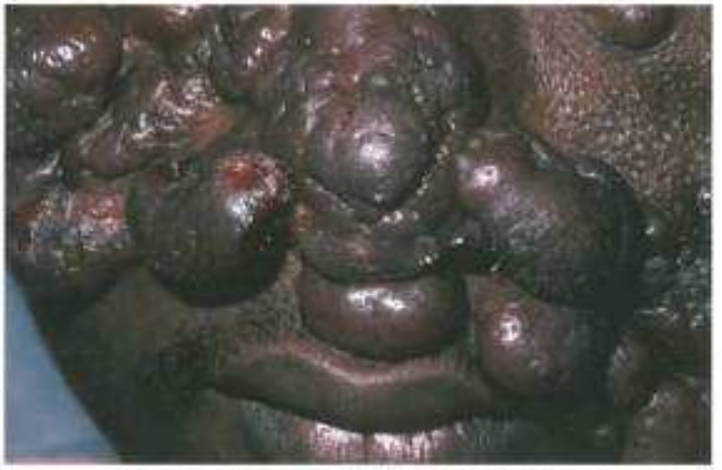


Fig. 17.30 Diffuse cutaneous leishmaniasis. Disfiguring large keloid-like nodules with nasal infiltration and ulceration, but without destruction of the nasal septum result from a superabundance of *L. aethiopica* parasites in the immunosuppressed. (Courtesy of Dr Barbara Leppard.)

AMERICAN MUCOCUTANEOUS LEISHMANIASIS

Mucocutaneous leishmaniasis is a complex chronic destructive mucocutaneous disease caused by *L. braziliensis* and its subspecies *L. mexicana*.

Aetiology

It is most common in the damp forests of South and Central America although it is becoming increasingly peri-urban and opportunistic using hosts such as dogs and donkeys. It is a chronic destructive disorder of the skin that ultimately spreads to the mucous membranes of the upper respiratory tract in about a third of the patients. The incubation period is between 2 and 10 weeks. *L. viannia braziliensis* and *L. viannia guyanensis* are the common causes.

Clinical Features

Symptoms

The condition usually begins on exposed skin following a sandfly bite.

Morphology

It progresses from a papule, which enlarges to produce a firm, indurated plaque or nodule rather like cutaneous leishmaniasis but then continues to enlarge becoming several centimetres in diameter. It has a characteristic raised border and usually ulcerates centrally (Fig. 17.31). If it does not, it

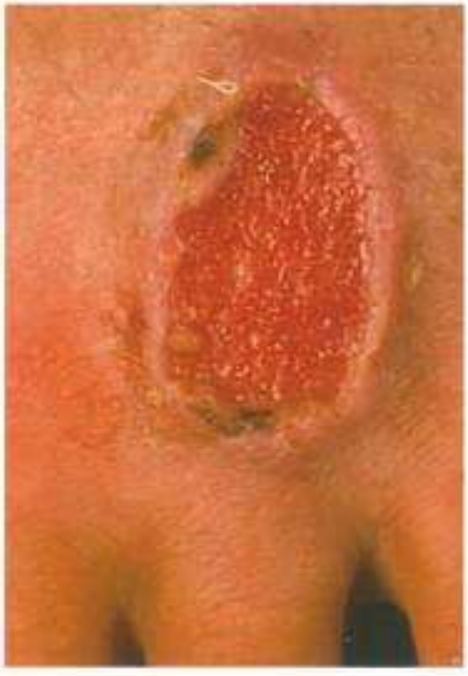


Fig. 17.31 Cutaneous leishmaniasis. This was due to *L. mexicana*. The ulcers are usually much larger than Old World leishmaniasis. The raised border is characteristic. (Courtesy of Prof. Rod Hay.)

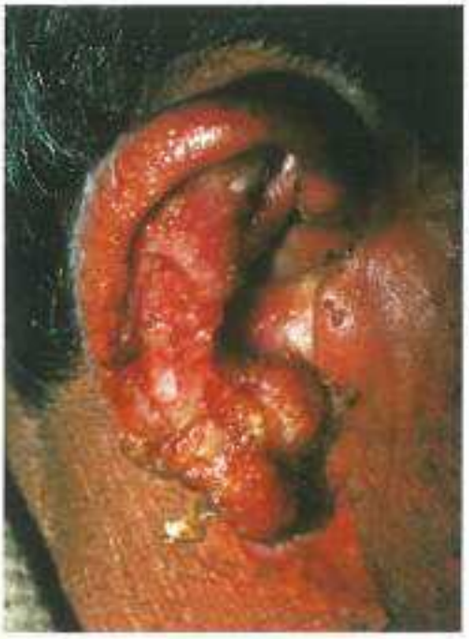


Fig. 17.32 Mucocutaneous leishmaniasis. There is a weeping, crusted and eroded plaque involving the skin and cartilage caused by *Leishmania mexicana*. This variety is classically seen in forest workers who collect gum from chicle trees and sleep on the forest floor. (Courtesy of the Institute of Dermatology.)

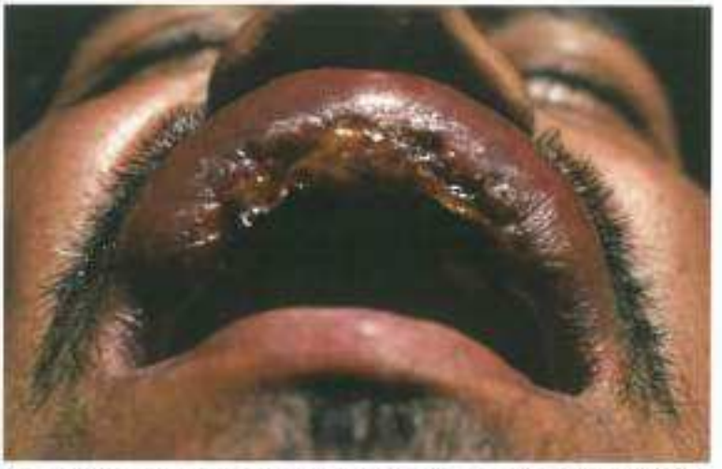


Fig. 17.33 Mucocutaneous leishmaniasis (Espundia). There is swelling of the lip due to infiltration and ulceration, with involvement of the mucocutaneous border and scarring of the nostrils. (Courtesy of Dr Anthony Bryceson.)

has a nodular verrucous or a sporotrichoid appearance if it spreads via the lymphatics. Secondary infection is common in the lesions and they tend to bleed. Regional adenitis is present. The condition tends to heal spontaneously over a matter of several months.

Distribution

The *L. mexicana* complex, which most often infects people who work in the forests, affects particularly the sides of the face and behind the ears; lesions on the pinna may invade the cartilage (Fig. 17.32) and destroy it. It takes many years to heal. It also occurs in the limbs as does infection with the *L. braziliensis* complex. This variety is responsible for the large, deep, ulcerated type of lesion with a raised edge and the lesions are often fleshy and protuberant. They occur particularly along the lymphatics.

Systemic features

The cutaneous sores of *L. mexicana* or *L. braziliensis* complex may involve the mucous membranes after a few years. This usually begins in the nasal mucosa, which are inflamed, swollen and ulcerated. Gradually the cartilage and nose are destroyed, together with the lips (Fig. 17.33) and, ultimately, the pharynx, tonsils, mouth, tongue and even larynx are involved which interferes with nutrition and breathing. There is an appreciable mortality.

Management of Leishmaniasis

The organism may be demonstrated in smears taken from the sore and stained with Giemsa. Alternatively Leishman–Donovan bodies may be seen within enlarged histiocytes in histopathological sections (Figs 17.34 and 17.35) from a skin biopsy and in kala-azar also in bone marrow, lymph node or splenic puncture tissue. The organism may be cultured on Novy–MacNeal–Nicolle's (NMN) medium. The leishmanin test is positive in all forms except the diffuse nodular type, but does not distinguish between past and present infection. PCR is generally positive.

Cutaneous leishmaniasis is not easy to treat:

- most sores heal spontaneously but smaller lesions may be excised or treated with cryotherapy
- 15% paromomycin ointment and 12% methylbenzethonium chloride in white soft paraffin has been reported as successful
- intralesional sodium stibogluconate
- systemic treatment with pentavalent antimonials with sodium stibogluconate or meglumine antimoniate intravenously or intramuscularly
- Miltefosine (a phosopholipid derivative) is a novel oral agent.

Mucocutaneous disease, kala-azar and severe cutaneous disease are treated with systemic pentavalent antimonials (sodium stibugluconate and meglumine antimionate). Side-effects are common, including nausea,

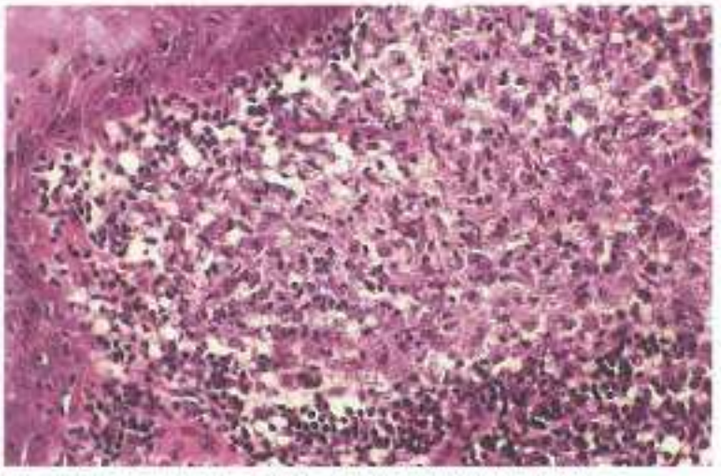


Fig. 17.34 Leishmaniasis. This dermal papilla is expanded by a dense inflammatory cell infiltrate including many macrophages containing amastigotes.

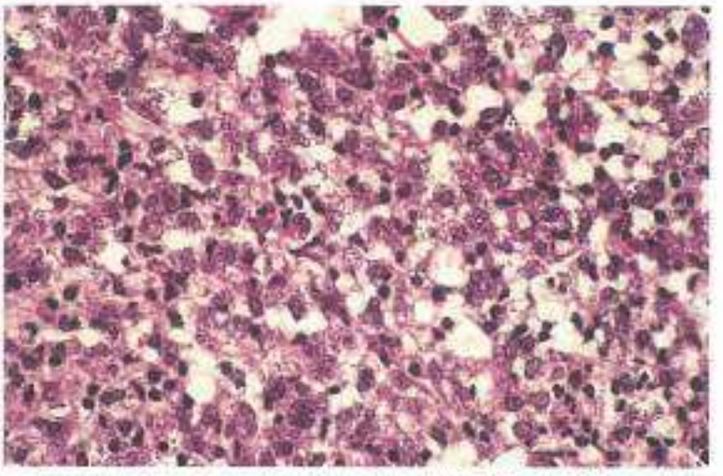


Fig. 17.35 Leishmaniasis. The Leishman–Donovan bodies are evident as small spherical bodies within the macrophages.

headache, arthralgias, cardiotoxicity (prolongation of the QT interval and ST-T were changes) thrombocytopenia, hepatitis, pancreatitis and rarely renal failure, and pain at the injection sites and glucantine is often used instead. Other agents include itraconazole and amphotericin.

Schistosomiasis (Bilharzia)

A serious systemic helminthic infection caused by one of several species of trematode in which the skin is only involved incidentally.

Aetiology

Schistosomiasis is caused by a fluke (a flat worm) that in the human lives in pairs in the venous system of the liver, rectum or bladder and can travel via the bloodstream to other tissues. The eggs are excreted in the faeces, urine or sputum. The flukes have a complicated life cycle. The eggs must enter water and develop into miracidia, which seek out schistosome-specific freshwater snails, their intermediate host. Motile cercariae develop in the snails and are released into water. The free-swimming cercariae penetrate intact human skin and pass into the bloodstream and then mature as larvae in the intrahepatic portal veins; eggs are deposited in the pelvic veins. *Schistosoma mansoni* and *Schistosoma japonicum* localize in the large gut and their eggs are passed in the faeces. *Schistosoma haematobium* invades the bladder and sometimes the rectal veins and the eggs are passed through the urine. Alternatively, the motile cercariae may have a resting phase in aquatic plants or fish and are later eaten. The ova make their way out of the veins into the surrounding tissues and cause granulomas. *S. mansoni* is common in Africa particularly around the Nile delta and in Central and South America, especially in northeastern Brazil. It is almost eradicated from the Caribbean. *S. japonicum* occurs in the Far East, China (where it is a major public health problem), Japan (nearly eliminated) and the Philippines. *S. haematobium* is common in Africa, India and the Middle East, particularly in Egypt around the Nile delta. *S. mekongi* is found in Southeast Asia and *S. intercalatum* in West and Central Africa. Visitors who swim in infested lakes or rivers are at risk.

Clinical Features

There are four types of cutaneous involvement.

- **Schistosomal dermatitis** This is an itchy papular eruption that occurs on the exposed parts in swimmers following cercarial penetration of the skin. It is indistinguishable from cercarial dermatitis, known as *swimmer's itch*. The urticarial reaction begins to regress after a few days although the patient may continue to itch for 2 to 3 weeks.
- **Urticarial reactions (*Urticarial fever or Katayama disease*)** These are particularly common and severe in *S. japonicum* infection. About a month or two after penetration of the skin by the cercariae an urticarial reaction occurs predominantly on the trunk associated with fever, malaise, arthralgia, diarrhoea, abdominal cramps and purpura. The liver and spleen are enlarged and there is eosinophilia.
- **Paragenital granulomas and fistulous tracts** This is most common in areas of high endemicity. There are firm granulomatous masses, which may become extensive and are associated with communicating fistulas and sinuses, on the perineum, external genitalia (Fig. 17.36) and buttocks.
- **Ectopic cutaneous schistosomiasis** Ova and flukes in pairs may become dislodged and embolize to the lung, conjunctiva, central nervous system or skin. Ectopic cutaneous disease usually involves the trunk including around the umbilicus; there are small, firm, ovoid, flesh-coloured papules that become confluent and form plaques with irregular contours, which may scale, ulcerate and become pigmented.

Systemic features

The importance of the disease is that it leads to the chronic fibro-occlusive disease of the liver (with cirrhosis and portal hypertension), intestine and urinary tract (eventuating in obstructive hydronephritis and carcinoma of the bladder) and therefore must be diagnosed and treated early.

Management

The characteristic ova may be found in the stools, urine or rectal snips. There is also a bilharzial skin test, complement fixation and enzyme-linked immunosorbent assays (ELISA). Histology from a skin, liver or mucosal biopsy shows epithelioid cell granulomas and schistosomal eggs (Fig. 17.37). Praziquantel 20 mg/kg twice daily (three times daily for *S. japonicum*) is curative in the early stages.

Dracunculosis

Dracunculosis is a chronic infection with *Dracunculus medinensis*, a large nematode that ultimately discharges through the skin.

Aetiology

The disorder is caused by a Guinea worm, *D. medinensis*, which is endemic in dry, parched areas of the world, particularly Arabia, Pakistan, India, Africa (especially Ghana and the Sudan), Indonesia and New Guinea. The female is about 1 to 2 mm wide and between 50 and 120 cm long. Males

Fig. 17.36 Schistosomiasis. The external genitalia are involved, with granulomatous masses with sinuses and fistulae. (Courtesy of Dr Catriona Henderson.)

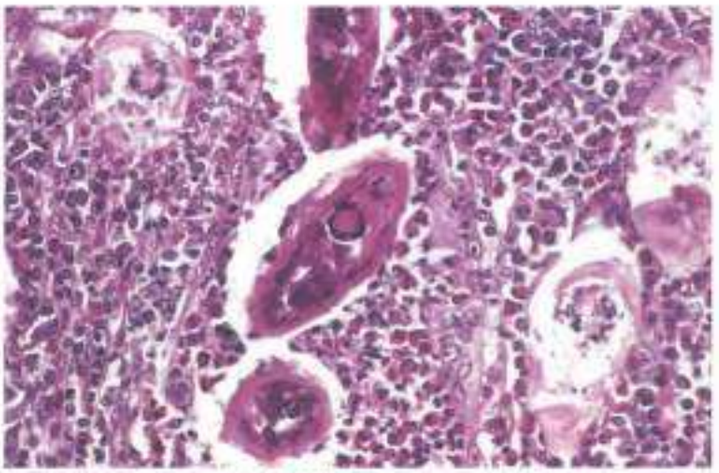


Fig. 17.37 Schistosomiasis. Epithelioid granulomas and schistosomal eggs are present.

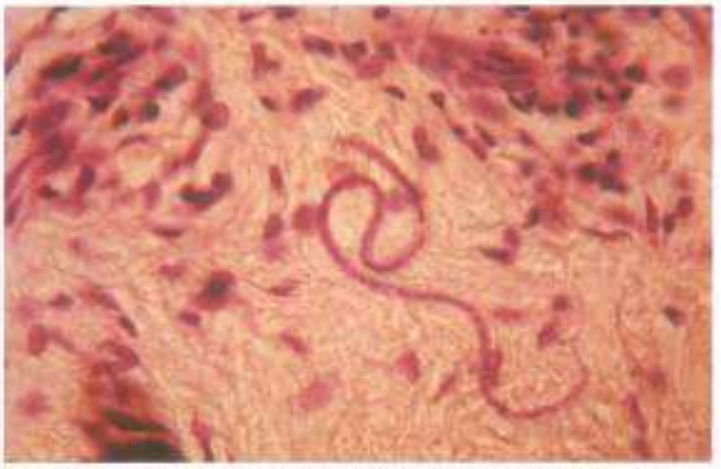


Fig. 17.38 Dracunculiasis. The Guinea worm produces a serpiginous track in the subcutaneous tissue before emerging. (Courtesy of Dr Martin Wood.)

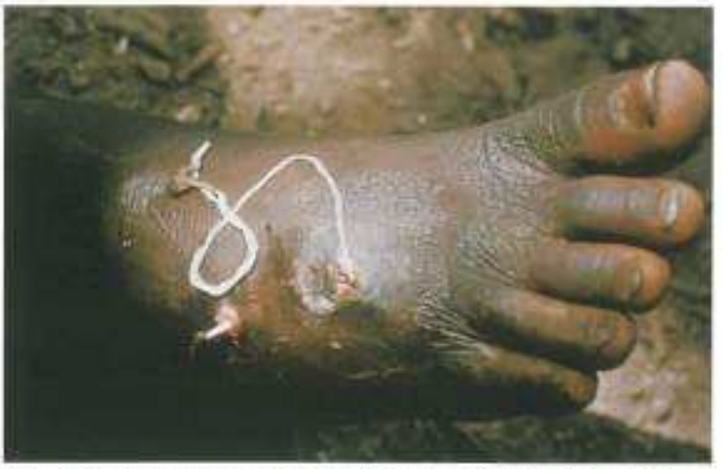


Fig. 17.39 Dracunculiasis. The adult female nematode is evident emanating from a swelling on the foot of a child. (Courtesy of Dr R. Muller.)

are very much shorter. Humans are infected by drinking water contaminated with infected water fleas, usually in poor rural areas where drinking and washing are communal at village wells. Larvae in the fleas are released in the human gut and migrate to retroperitoneal tissue, where they mature and mate. They take about 8 months to become adults. The males die but the females migrate, usually to the lower limbs, and discharge millions of larvae through an ulcerated skin lesion. The larvae can survive several days especially in water, where water fleas of the *Cyclops* sp. become infected.

Clinical Features

Symptoms

The condition is clinically silent until 24 hours before the female reaches the subcutaneous tissues (Fig. 17.38) and breaks through the skin, when there is severe toxaemia with urticaria or other erythematous eruptions, respiratory symptoms, diarrhoea, malaise and fever.

Morphology

A papule evolves into a blister, which, on contact with water, discharges large numbers of motile larvae from a loop of uterus of the worm. The systemic reaction subsides at this time. The adult female worms may then appear (Fig. 17.39) and be extracted. It may be felt as a firm tortuous cord in the tissues. The larvae are discharged over a number of weeks and then the worm dies and is either absorbed or calcified.

Distribution

The lesion usually occurs on the leg, which is itchy and oedematous.

Systemic features

Secondary infection through the broken skin is common and leads to cellulitis, lymphangiitis, regional adenitis and septicaemia. Tetanus may supervene.

Management

Diethylcarbamazine, thiabendazole and metronidazole are effective in the early stages but do not help once the adult worm has appeared on the skin. The worm, however, may be extracted using a matchstick and gentle massage of the skin towards the aperture over several hours.

Filariasis

Filariasis is caused by a nematode (roundworm). It results in lymphangiitis, lymphadenitis and fever and ultimately in chronic elephantiasis.

Aetiology

The disorder is spread from person to person by infected mosquitos. It is caused by the nematodes *Wuchereria bancrofti* (worldwide), *Brugia malayi* (South and East Asia), and *B. timori* (Indonesian islands). It occurs between latitudes 45° North and 25° South, particularly in Africa, Asia, the Pacific and the northeastern part of South America. The adult filaria live and mate in the lymphatics of the extremities and external genitalia. About a year after infection, the fertilized females discharge microfilaria into the peripheral blood in a cyclical manner, mostly at night between midnight and 2 a.m. These microfilaria are ingested by biting mosquitos. They lose their sheaths in the stomach of the mosquito and proceed to the thoracic muscles. Metamorphosis occurs and the mature larvae reach the labella and are then ready for transmission to the lymphatics of another human via a bite. The adult worms in the lymphatics of the human cause lymphatic obstruction through recurrent inflammation. They have little effect in the bloodstream except that in the lungs they may cause a tropical pulmonary eosinophilia.

Clinical Features

Symptoms

There is usually an incubation period of approximately 1 year (swifter in susceptible individuals arriving in a highly endemic area) followed by recurrent monthly episodes of fever, lymphangiitis of the legs and scrotum and lymphadenitis, which become less severe and less frequent as time goes by. Ultimately, fibrosis and obstruction of the subcutaneous tissue leads to irreversible elephantiasis of the external genitalia and legs.

Morphology

Lymphangiitis, urticarial and erythema nodosum-like lesions occur. Ultimately, the skin becomes thickened, coarse, dry and cracks. Secondary infection is common, resulting in chronic ulceration.

Distribution

The legs (Fig. 17.40) (since female mosquitos fly near the ground) and external genitalia.

Systemic features

In the acute early stages there are recurrent episodes of fever and lymphangiitis lasting a week at a time and sometimes orchitis and epididymitis.

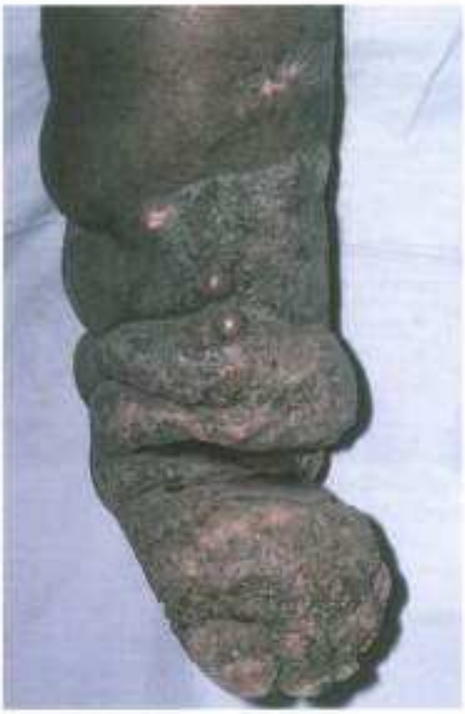


Fig. 17.40 Filariasis. There is pronounced warty lymphoedema from repeated lymphangitis caused by the filarial worms, transmitted by mosquitos. Multiple bites are required. (Courtesy of Dr Barbara Leppard.)

Fig. 17.41 Podoconiosis. Africans who never wear shoes are susceptible to chronic trauma and secondary bacterial sepsis in rural areas. Ultimately, lymphoedema may result, followed by warty thickening of the skin. (Courtesy of Mossy Foot UK and Dr Claire Fuller.)

Management

The clinical picture is suggestive but the microfilaria are demonstrable in blood samples taken at midnight. Lymph node biopsy may be helpful. A filarial intradermal test is available. There is a serological test and polymerase chain reaction analysis of the blood may be positive. Microfilariae are sensitive to diethylcarbamazine used in the same way as for onchocerciasis but the drug has little effect on adult worms. Side-effects of nausea, vomiting, giddiness, headache and drowsiness are common and an acute allergic reaction to the destruction of microfilaria may occur. Diethylcarbamazine is used as a diagnostic test in that it causes release of microfilaria into the blood 1 hour after a single dose of 100 mg. Lymphatic filariasis and onchocerciasis may coexist. Ivermectin is also effective against microfilaria.

An elephantiasis-like appearance may also occur in chronic idiopathic lymphoedema (Ch. 23) and also in *podoconiosis* (endemic non-filiarial elephantiasis). This is described in the volcanic highlands of tropical Africa, where patients walk barefoot. Chronic trauma and secondary bacterial infection may damage the lymphatics, causing lymphoedema and subsequently warty elephantiasis of the skin (Fig. 17.41). Initially, the symptoms are of recurrent attacks of nocturnal burning and itching of the lower leg and foot, usually after a long journey, sometimes with fever and lymphadenopathy. Chronic scratching ensues, followed by lymphoedema with splaying of the forefoot and brushing of the big toes together with walking. Oozing from the skin attracts flies and gradually elephantiasis ensues. The morbidity from these conditions is considerable.

Loiasis

An infection of the subcutaneous tissue, viscera and eye with the Loa loa worm, which is transmitted during the day by infected bloodsucking flies.

Aetiology

The larvae of the loa worm are transmitted from person to person by *Chrysops* sp. (deer, horse and mangrove flies) via a puncture from the proboscis. It particularly occurs in hill houses at the level of the forest canopy or in houses in clearings. After about a year, the adult worms are found under the skin or in the conjunctivae and about 5 months later microfilaria are found in the blood.

Clinical Features

Symptoms

Wandering adult worms may give rise to a pricking, itching or creeping sensation. In the conjunctiva, they may be visualized crossing the eye, accompanied by considerable irritation and often swelling of one eyelid. Calabar swellings are painful.

Morphology and distribution

- **Calabar swellings** In susceptible patients, distinctive rapidly developing painful swellings, up to 5 cm in size, occur mainly on the arms and hands when the worm is in the subcutaneous tissue, and last for a few days.
- **Worm migration** About a year after the bite, the adult worms begin to wander around the fascial planes, enter the lymphatics and proceed via the bloodstream into the viscera and lungs. They make frequent journeys through the skin which may be visualized particularly on the fingers, trunk, scalp, penis and eyelids and conjunctivae (Figs 17.42).

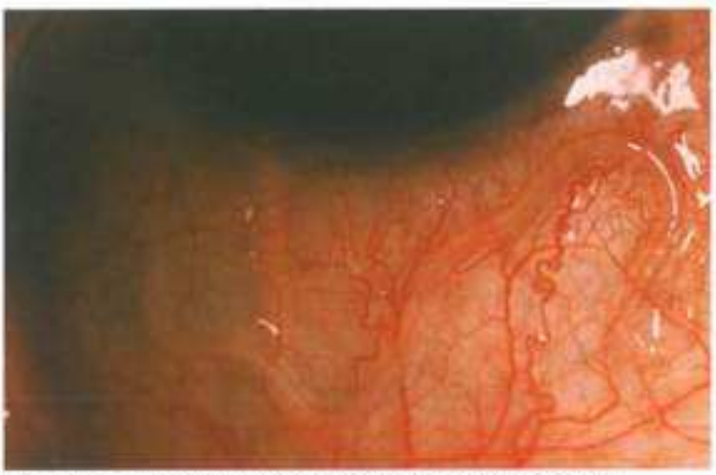


Fig. 17.42 Loiasis. Adult worms wander through the skin, eyelids and conjunctivae and may be visualized. (Courtesy of Teaching Aids at Low Cost, Institute of Child Health, London.)

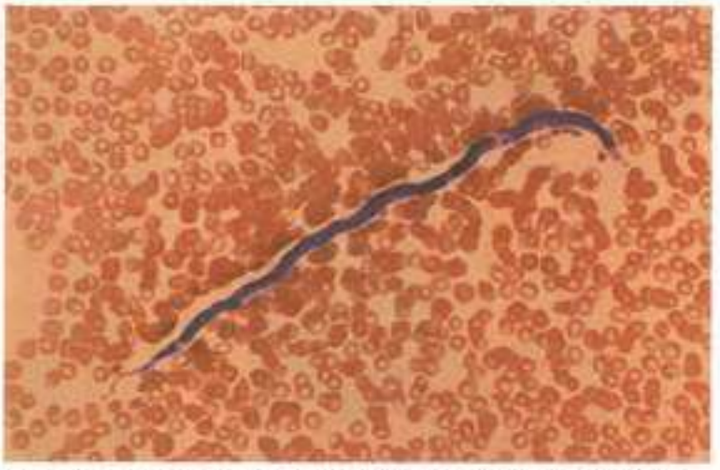


Fig. 17.43 Loiasis. The microfilaria are visible in the peripheral blood during the day. (Courtesy of Teaching Aids at Low Cost, Institute of Child Health, London.)

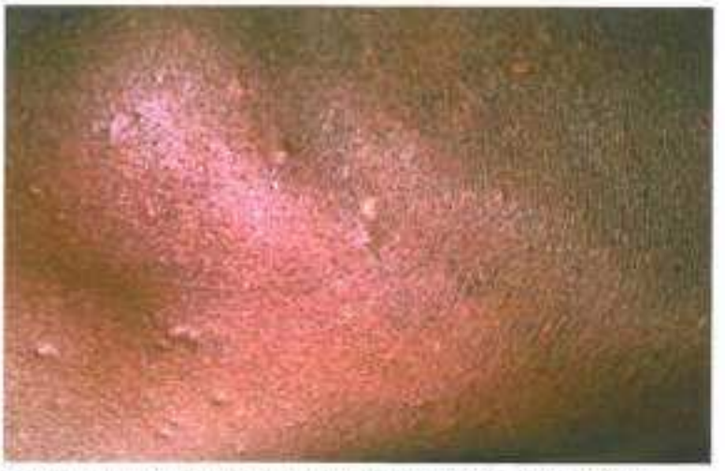


Fig. 17.44 Acute papular onchodermatitis. In the early stages, an itchy papular eruption occurs particularly on the limbs. (Courtesy of Prof. Rod Hay.)

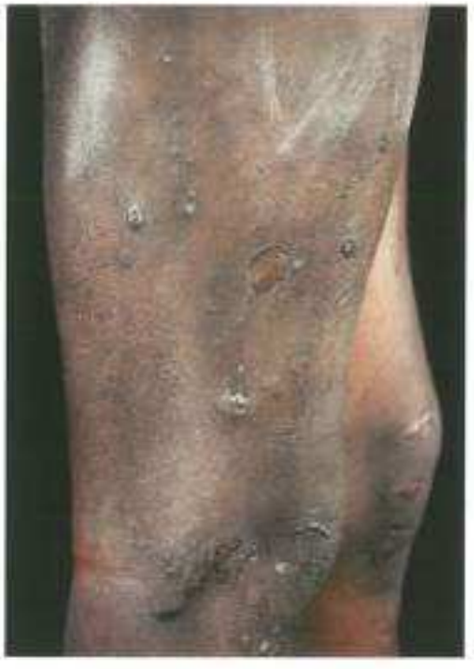


Fig. 17.45 Onchocerciasis. The skin is dry, pigmented and excoriated. It is intensely pruritic. (Courtesy of the late Dr Roger Clayton, St Mary's Hospital.)

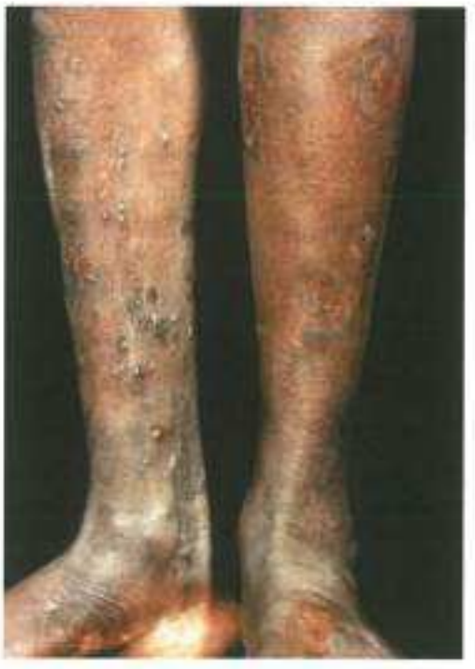


Fig. 17.46 Onchocerciasis. Excoriated pruriginous nodules are present on both legs. Lichenification is present over the fronts of the ankles. (Courtesy of St Mary's Hospital.)

- **Allergic manifestations** Angioedema and eosinophilia are common.
- **Calcification** The adult worms may live for several years before dying and becoming calcified.

Systemic features

The peripheral nerves and central nervous system may be involved, with encephalitis and meningitis. Glomerulonephritis is not uncommon.

Management

Microfilaria are visible in the peripheral blood (Fig. 17.43) during the day and may be stained with Giemsa. There is a filarial skin test as well as a complement fixation test. One dose of diethylcarbamazine is usually curative but allergic reactions do occur and encephalitis may result in patients with very heavy infections. Ivermectin is effective against the microfilaria.

Onchocerciasis

An infection of the skin and eyes with *Onchocerca volvulus*, a filarial worm transmitted by a small black fly.

Aetiology

O. volvulus infests rural tropical Africa, Arabia and central and northern South America. It is transmitted by the tiny black fly of the Simuliidae family. They are known as 'buffalo gnats', because they have a hump-backed stance like buffalo. They breed by fast-flowing, well-oxygenated rivers, which provide the high oxygen tension required for the larvae of *O. volvulus* to thrive during its obligatory aquatic phase. It is the largest of the insect-borne filaria. Females may measure up to 70 cm in length. The microfilaria are not present in the blood but reside in the connective tissue and lymphatics of the skin and in the eye.

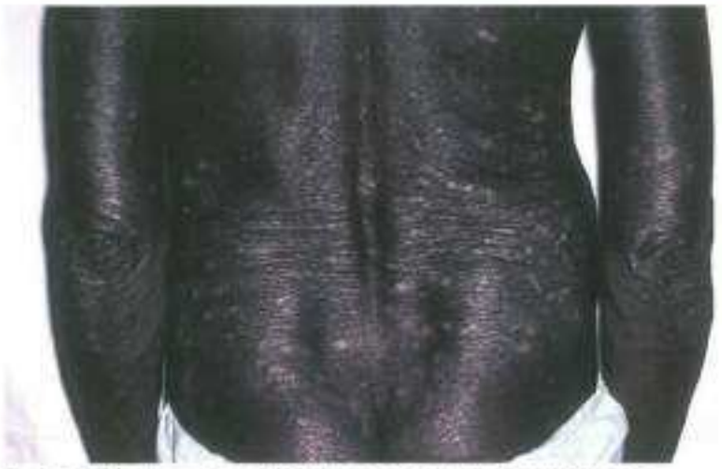


Fig. 17.47 Onchocerciasis. The intense pruritus results in scratching and chronic lichenification of the skin, which eventually hangs in folds. (Courtesy of Dr Barbara Leppard.)

Fig. 17.48 Onchocercomata. These painless, mobile, calcified lumps are the result of granulomatous reaction around the parasites. (Courtesy of Dr Anthony Bryceson.)

Fig. 17.49 Onchocerciasis. The microfilariae may be demonstrated in strips of skin in saline. (Courtesy of the late Dr Roger Clayton, St Mary's Hospital.)

Clinical Features

Symptoms

The African gnat bites are painful. The condition is itchy.

Morphology and distribution

An acute papular eruption (Fig. 17.44) occurs on the legs initially. This disappears but the pruritus (Fig. 17.45) continues and pruriginous nodules (Fig. 17.46), lichenification, pigmentation and scarring result. It is particularly prominent over the buttocks, thighs and legs. The skin gradually loses its elasticity and becomes dry, scaly, atrophic and depigmented. As the skin becomes more thickened (Fig. 17.47), furrows develop and there is a tendency for the skin to begin to hang down in some patients, which is known as 'hanging groins'. Mature worms and microfilaria are found in large granulomatous nodules, which vary between 3 and 35 cm in size and represent a fibrous reaction around the parasites with calcification. These occur predominantly on the trunk and legs in Africa and in the scalp in Central America, probably owing to the different sites of entry of the organisms. These painless, mobile lumps are known as *onchocercomata* (Fig. 17.48) and are usually found close to bony prominences.

Systemic features

In the earlier stages, keratitis, iritis and choroiditis occur. Later this may result in blindness, hence the alternative name 'river blindness' because the gnats breed so close to rivers.

Management

The microfilaria may be found in skin snips placed in physiological saline (Fig. 17.49). The microfilaria migrate rapidly from the skin and swim freely in the saline. A skin biopsy may be helpful. There is a relative eosinophilia. The microfilaria may be visualized in the anterior chamber of the eye. Ivermectin has replaced diethylcarbamazine and suramin, which could produce severe hypersensitivity reactions, as the drug of choice.

Ancylostomiasis (Hookworm)

An infection caused by penetration of *Necator americanus* or *Ancylostoma duodenale* through intact skin of those who walk barefoot; it causes a 'ground itch' with migration via the blood to the lungs (*Loeffler's syndrome*) and subsequent residence in the duodenum and jejunum, causing anaemia and malabsorption.

Aetiology

N. americanus occurs in subtropical and tropical climates of south southern Asia, central and southern Africa, in the New World and Polynesia. *A. duodenale* occurs around the Mediterranean coastline, in central and northern Asia and in China, Indonesia and Japan. The adult hookworm lives in the jejunum, causing bleeding, anaemia, gastrointestinal symptoms and malabsorption. The eggs are deposited via the faeces into the soil where they can survive; under favourable conditions of warmth and humidity, the eggs hatch into infective larvae, which are capable of penetrating human skin. Walking barefoot in plantations and cultivated fields is the commonest way of becoming infected.

Clinical Features

Symptoms

Severe pruritus on the feet with a rash (ground itch).

Morphology and distribution

An erythema and a papular vesicular rash occurs on the feet. Occasionally, there is generalized urticaria.

Systemic features

As the larvae pass through the lungs, a patchy pneumonitis with eosinophilia may occur (Loeffler's syndrome). The patient experiences cough, wheeze and dyspnoea for several days. The presence of the adult worms in the jejunum and duodenum is responsible for the anaemia, hypoproteinaemia and changes in the skin and hair, which are similar in advanced disease to those of kwashiorkor.

Management

The diagnosis is established by finding the characteristic eggs in the faeces.

A 3-day course of albendazole or mebendazole is effective. The ground itch may be treated symptomatically with crotamiton with 1% hydrocortisone with or without oral antihistamine.

Strongyloidiasis

Strongyloidiasis is a nematode infection with *Strongyloides stercoralis*, which causes diarrhoea and malabsorption following a dermatitis or ground itch at the site of penetration of the skin with the larvae. Migration of the larvae subcutaneously is known as *larva currens*.

Aetiology

S. stercoralis has a similar life cycle to hookworm but is found in the warm, damp climates especially of southeastern Asia (and still infects those who were prisoners of war in Japanese camps in World War II) and the southeastern USA. The adult male and female are 3 mm long and live in the duodenum and jejunum, producing diarrhoea and malabsorption. Their larvae are excreted via the faeces and are found in the soil. The larvae are subsequently able to penetrate the skin and produce ground itch. Urticaria is common.

Clinical Features

Symptoms

A very itchy rash at the site of penetration of the larvae, usually the feet, and the patient may observe the larvae migrating through the skin.

Morphology

- A ground itch
- Urticaria
- Larva currens

An urticarial weal and flare is seen around the migrating larvae. They move at several centimetres an hour and may be invisible after several hours. They are found particularly on the buttocks and around the anus but are said to occur anywhere between the knees and the nipples. These tracks are several inches long and are linear or serpiginous (Fig. 17.50).

Systemic features

In heavy infestations, the patient is ill with diarrhoea and fluid and electrolyte imbalance, which may result in ileus and shock. Gram-negative septicaemia and pneumonia may supervene.

Management

The larvae are found in the faeces and jejunum. There is a strongyloides ELISA antibody test. There is often eosinophilia. Tiabendazole was the treatment of choice but albendazole and ivermectin are effective.

Larva migrans (Creeping eruption)

A serpiginous eruption caused by larvae of one of a variety of non-human-specific nematodes.

Aetiology

The ova of *Ancylostoma caninum* or *Ancylostoma braziliensis* are deposited in the soil from the faeces of infected dogs and cats. They survive particularly in sandy, shaded areas that are protected from extremes of temperature and dessication, in the Caribbean, central and southeastern USA, Africa, southeast Asia and South America. The larvae hatch out in the soil and penetrate human skin, often of holidaymakers walking or sitting on a contaminated beach.

Clinical Features

Symptoms

The patient observes an intensely itchy mobile track.

Morphology

There is one or several linear serpiginous tracks (Fig. 17.51) made by the hookworm larvae, which move a few millimetres a day, unlike larva currens of *Strongyloides* sp., which moves much more swiftly.

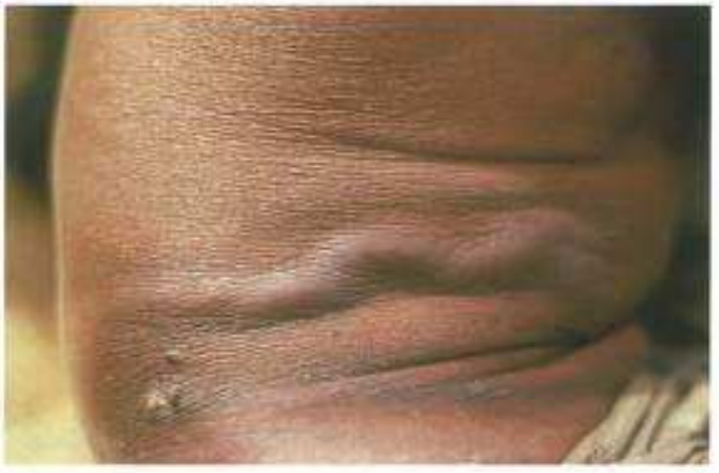


Fig. 17.50 Larva currens. The larvae of strongyloidiasis are excreted into the soil and subsequently penetrate the skin and migrate visibly through the skin. Adults live in the duodenum and jejunum and result in diarrhoea and malabsorption. (Courtesy of Dr Martin Wood.)

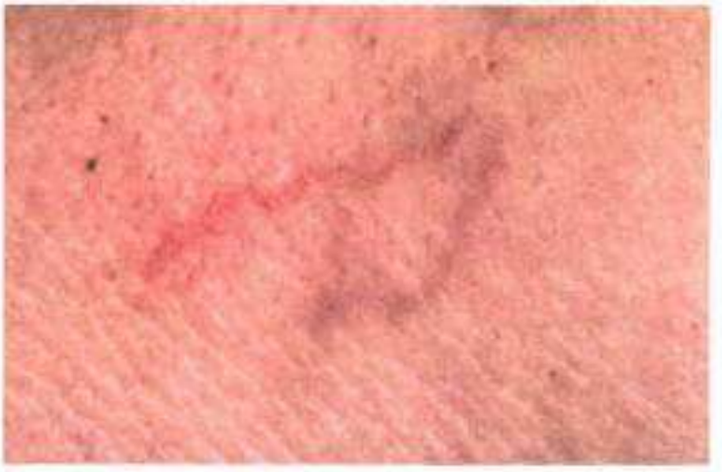


Fig. 17.51 Larva migrans. There is a fine serpiginous track. It is intensely itchy but responds to topical or oral thiabendazole and oral albendazole.

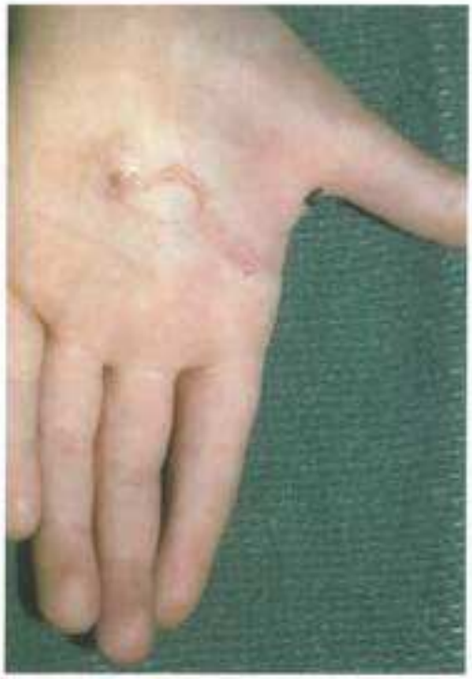


Fig. 17.52 Larva migrans. Linear mobile tracks occur. The disorder is caused by canine hookworm larvae penetrating the skin.

Distribution

The foot, buttock or hand (Fig. 17.52) are usual sites of entry.

Management

The diagnosis is clinical. A skin biopsy is not usually helpful because the worm is usually ahead of the biopsy site and not seen. The disease is self-limiting within a few weeks because the human is a 'dead end host'. However it responds to:

- 10% tiabendazole in a water-soluble base: a 500 mg tablet of tiabendazole is crushed and may be added to unguentum merck
- tiabendazole orally in a dose of 25 mg/kg for 2 days, but there are side-effects of gastrointestinal upset and dizziness
- albendazole 400 mg twice daily for 3–5 days
- ivermectin (200 mcg/kg for 2 days).

Larva migrans does not have any systemic effect and, therefore, should be distinguished from *visceral larva migrans*, which is caused by toxocariasis, a roundworm infection of dogs (particularly puppies) and cats, which is passed in faeces as eggs into the soil. The infection is ingested in contaminated food, water or soil (paticularly by children playing in public parks). There is eosinophilia, cough and dyspnoea, muscle pains, sometimes fever, failure to thrive, hepatomegaly and increased gammaglobulins. Cutaneous aspects of visceral larva migrans are usually generalized pruritus with urticarial and papular eruptions of the trunk.

Chromoblastomycosis

A chronic, warty cutaneous and subcutaneous infection with a fungus with pigmented hyphae.

Aetiology

Chromoblastomycosis (verrucous dermatitis) is caused by dematiaceous fungi, moulds with pigmented septate hyphae that are saprophytic on wood or soil and are found in rural areas in the Americas, Caribbean, India, Madagascar, Australia and Northern Europe. The organism enters via a wound (e.g. a splinter) and is most common in males who work outside bare legged. 90% are caused by *Fonsecaea pedrosoi*.

Clinical Features

Symptoms

A warty mass develops following an abrasion.

Morphology

Slow-growing exophytic lesions develop as a series of warty nodules (Fig. 17.53) and hyperkeratotic plaques (Fig. 17.54). Secondary ulceration may occur. They are usually painless unless secondary infection is present. There may be lymphatic spread and ultimately elephantiasis. Squamous cell carcinoma occasionally complicates a chronic lesion.

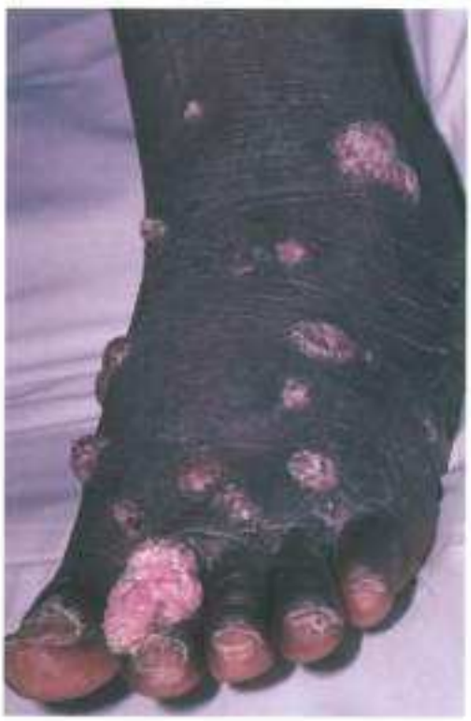


Fig. 17.53 Chromoblastomycosis. A series of warty (verrucous) nodules and plaques develop, usually on the feet, secondary to implantation of a dematiaceous fungus from the soil. (Courtesy of Dr Barbara Leppard.)

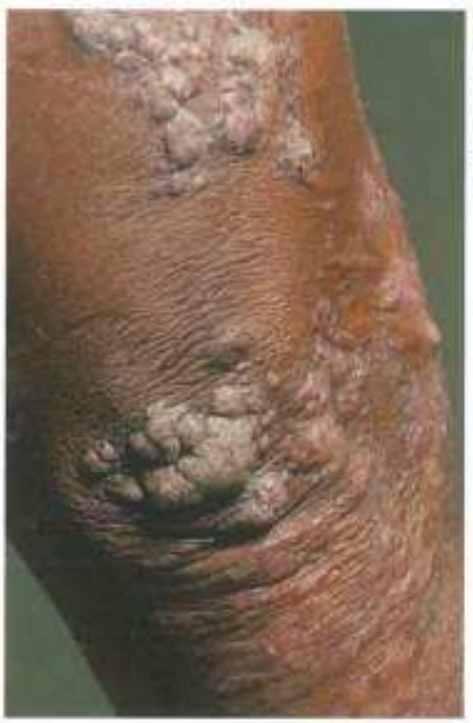


Fig. 17.54 Chromoblastomycosis. The lesions are slow-growing, warty plaques on a limb. Lymphatic spread and elephantiasis may result. (Courtesy of Prof. Rod Hay.)

Fig. 17.55 Chromoblastomycosis. There is acanthosis and pseudo-epitheliomatous hyperplasia overlying the upper dermis, in which pigmented, round spores are visible.

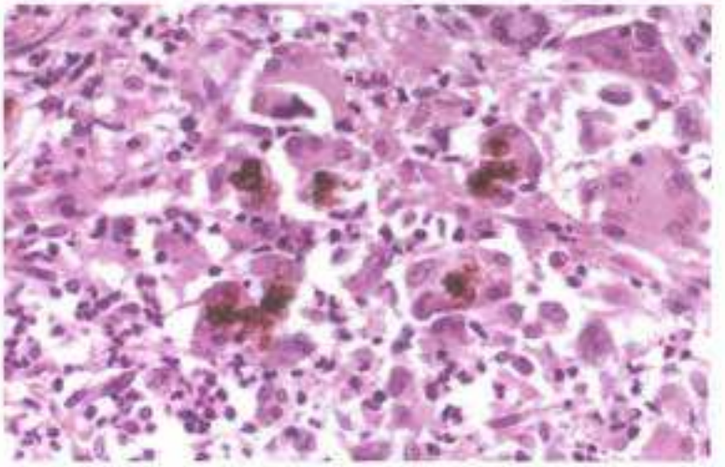


Fig. 17.56 Chromoblastomycosis. Dark brown spherical thick-walled spores are found in multinucleated giant cells and free in the tissues. They are known as Medlar bodies or 'copper pennies'.

Distribution

Usually the lower leg or feet but occasionally the hands, arms or trunk.

Management

Skin biopsy is helpful (Fig. 17.55). The diagnosis is made by finding septate dark brown cells in pairs or small clusters in tissues (Fig. 17.56) and exudates. The Grocott stain highlights the fungal walls. Various fungi may be grown on culture but their specific identification may be difficult.

Surgical excision is used for early lesions or cautery and diathermy. Itraconazole is effective, often combined with flucytosine. Terbinafine is reported as being effective. Amphotericin intralesionally and orally has been used. Posoconazole and voriconazole are increasingly being used.

Sporotrichosis

An infection of the skin caused by implantation of the dimorphic fungus *Sporothrix schenckii*, which subsequently spreads via the lymphatics and may become disseminated in the immunosuppressed.

Aetiology

S. schenckii is a saprophyte of decaying vegetation occurring in temperate and tropical climates in the Americas, Egypt, Japan and Southern Africa (particularly around the mines), acquired by accidental implantation. It is not contagious. In temperate climes, it may occur in gardeners from orchids or roses. There is high infectivity of cats and the immunosuppressed.

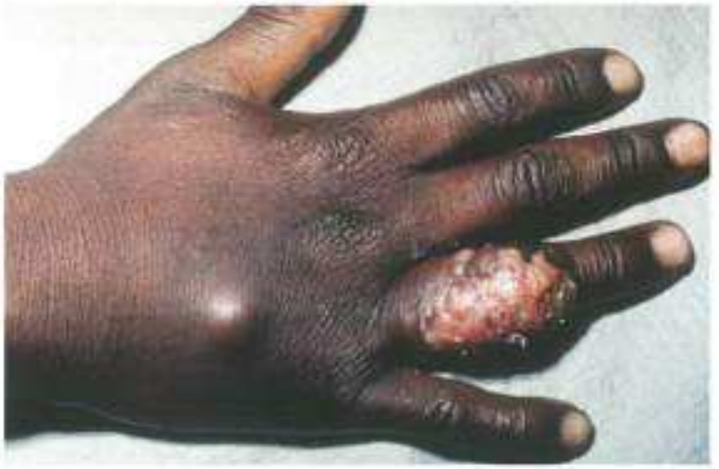


Fig. 17.57 Sporotrichosis. A warty, eroded swelling is present on the finger with a satellite lymphatic swelling, which is the beginning of 'sporotrichoid spread'. It is caused by implantation of the dimorphic fungus *Sporothrix schenckii*. (Courtesy of Dr K. A. Riley.)

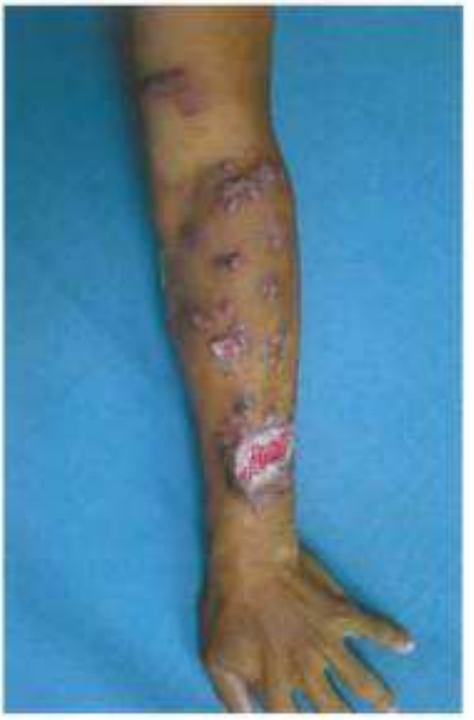


Fig. 17.58 Sporotrichosis. Several lesions may develop in a linear manner along the lymphatic drainage of the limb. (From Ramos-e-Silva, M., C. Vasconcelos, et al. 'Sporotrichosis'. Clinics in Dermatology 25(2): 181-187.)

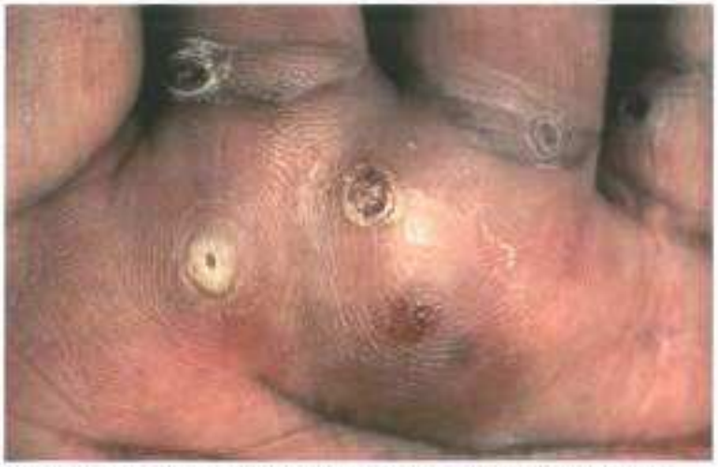


Fig. 17.59 Mycetoma. There is subcutaneous swelling with sinus tracts that drain pus and blood. (Courtesy of Prof. Rod Hay.)

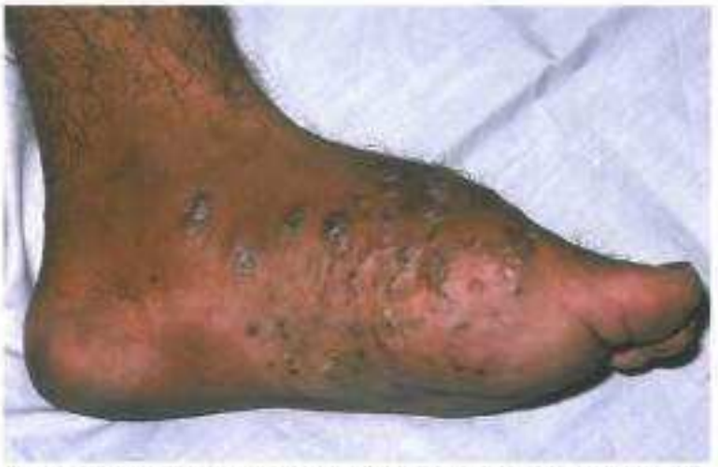


Fig. 17.60 Mycetoma. Many papules and nodules are present. The condition is caused by traumatic implantation of various soil fungi. Black grains are visible at sinus openings. (Courtesy of Dr Barbara Leppard.)

Clinical Features

Symptoms

There is usually a history of injury.

Morphology

Following an incubation period of 8 to 30 days, an indolent nodule develops (Fig. 17.57) subcutaneously; this spreads via the lymphatics to form a chain of lymphatic nodules ('sporotrichoid spread') (Fig. 17.58). Occasionally, the lesion may be limited to the point of inoculation in patients with a high degree of immunity. These varieties are sometimes accompanied by erythema nodosum.

Distribution

The hand is a common site.

Systemic features

Bloodstream dissemination may occur in the immunosuppressed (e.g. from alcoholism or HIV infection). There is a rare primary pulmonary form, possibly secondary to inhalation, which may occasionally disseminate to lymph nodes, bone, muscle, joints, viscera and the central nervous system.

Management

M. marinum and leishmaniasis may occur along lymphatics in a sporotrichoid manner and, therefore, enter the differential diagnosis. Direct examination of tissue is usually not helpful because of the limited number of organisms present. However, the fungus grows quite readily on Sabouraud's medium. The disorder may be treated with potassium iodide 10 drops three times daily after meals until the eruption is cleared or with amphotericin intravenously or itraconazole orally (100–200 mg daily for 3–6 months).

Mycetoma

Mycetoma is a chronic granulomatous fungal infection of the subcutaneous tissue, skin and bone, usually following an injury to the foot; it is characterized by tumefaction, sinuses and draining abscesses in which are found granules of the implanted soil fungi.

Aetiology

The condition is caused by traumatic implantation of saprophytic soil organisms, which include eumycotic true fungi with broad, thick, septate branching hyphae (e.g. *Pseudallescheria boydii*, which exhibits white granules, and *Madurella grisea*, which has dark granules), aerobic actinomycotic organisms with very thin, Gram-positive, branching filaments (e.g. *Nocardia braziliensis*, *Streptomyces maduraе* and others) and occasionally certain lower bacteria including *Proteus* and *Pseudomonas* sp. Mycetoma occurs in rural areas of India especially from acacia tree thorns (*Madura foot*), Sudan, southern Asia and tropical Central and South America in those who walk barefoot, particularly males.

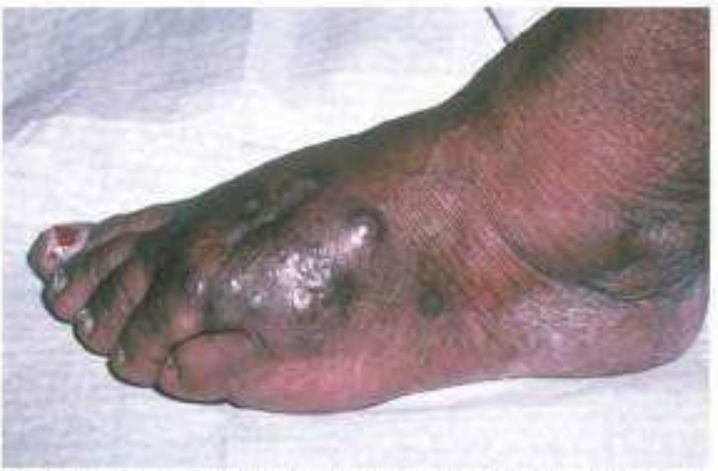


Fig. 17.61 Madura foot. The foot is commonly involved since it is easily injured and invaded by fungus. (Courtesy of Prof. Rod Hay.)

Clinical Features

Symptoms

There is a painless swelling and discharge from the skin.

Morphology

The subcutaneous swelling has sinus tracts (Fig. 17.59) that drain blood and pus.

Distribution

Mainly the lower leg, foot (Figs 17.60 and 17.61), hand and shoulders (from carrying loads on the back).

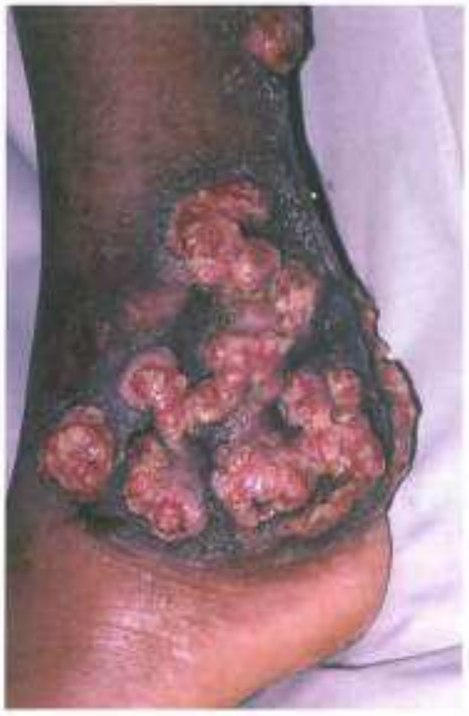


Fig. 17.62 Mycetoma. Many nodules develop, some of which break down and discharge pus, which contain the grains in this case of *Aspergillus*. Osteomyelitis, arthritis and gross destruction of bone may develop. (Courtesy of Dr Barbara Leppard.)

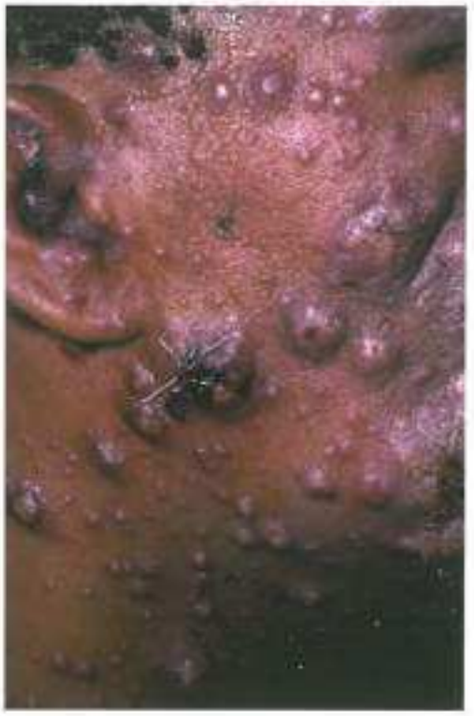


Fig. 17.63 Histoplasmosis. Cutaneous lesions (molluscum-like papules, nodules, abscesses and ulcers) occur in the immunosuppressed. This patient was HIV positive. It is primarily a respiratory disorder from inhalation of *Histoplasma capsulatum*, but may disseminate to the skin. (Courtesy of Dr Barbara Leppard.)

Systemic features

Gradually there is extension (Fig. 17.62), which continues to the bones and joints giving rise to periostitis, osteomyelitis and arthritis. Gross destruction and deformity may occur. Amyloid may result in chronic disease.

Management

Fungal colonies may be seen microscopically in the granules that drain from the sinus tracts. Tissue can be teased out from deep, skin biopsies and examined in potassium hydroxide preparations or cultured. Mycetoma is difficult to eradicate. There is a high level of disability. Treatment is prolonged and compliance often poor. Resistance is common. In general *Actinomycetes* sp. are potentially curable, but black grain fungi are not. Infections with *Actinomycetes* sp. respond partially to penicillin, sulphonamides, streptomycin, tetracyclines or rifampicin. Amikacin has been used in nocardial infections. Amphotericin is used for fungal causes of mycetoma, (not very effective). Itraconazole and voriconazole have also been used. Imipenen, a carbapenen with broad antimicrobial activity resists hydrolysis by β-lactamases (*N. brasiliensis*, the most common cause in South America and Mexico is a β-lactamase producer) may be helpful.

Surgery is used in early lesions and probably is the treatment of choice if the lesions can be excised without too much destruction. Amputation is sometimes required.

Histoplasmosis (Darling's disease)

A highly infectious endemic, primarily respiratory, granulomatous disorder caused by *Histoplasma capsulatum*, a saprophytic fungus, which may cause skin lesions in its rare disseminated form, which usually occurs in those with altered T cell immunity, especially AIDS.

Aetiology

H. capsulatum is a dimorphic fungus, which in its yeast phase measures 2–5 μm in *H. capsulatum* var. *capsulatum* and 10–15 μm in *H. capsulatum* var. *duboisii* and consequently histoplasmosis is known as small and large forms, respectively. The fungus is a saprophyte found in the soil, particularly that contaminated with chicken feathers or droppings but also associated with bats and starlings. Infection is through inhalation of airborne conidia, affecting the lungs in a manner reminiscent of tuberculosis. The fungus is intracellular and parasitizes the reticuloendothelial system and other organs, including the kidney and central nervous system. The small form is widespread in temperate and tropical climates, particularly the Americas (highly endemic in Mississippi and Ohio), Africa, the Far East and Australasia. The large form is found in Africa only. It affects children or adult male agricultural workers. There are four types of infection: an acute self-limiting pulmonary type with fever, rigors and a non-productive cough; a chronic pulmonary type; and a disseminated AIDS-defining type. Skin lesions are more common in this type following dissemination from the primary pulmonary source. Direct inoculation (the fourth type) is very rare.

Clinical Features

Symptoms

Pulmonary symptoms may or may not be present.

Morphology

The skin lesions are varied and may be papules, nodules (Fig. 17.63), ulcers, abscesses, granulomas or even cellulitic type lesions, particularly in the immunosuppressed.

Distribution

Anywhere, including the face (Fig. 17.64).

Management

The diagnosis is confirmed by finding intracellular yeasts in the sputum, peripheral blood, bone marrow and tissue biopsy material (Fig. 17.65). The organism may be cultured and there are serological tests for histoplasmal antigens. The diagnosis is usually made following investigation of the pulmonary symptoms. The organisms are responsive to amphotericin, itraconazole, fluconazole and voriconazole.

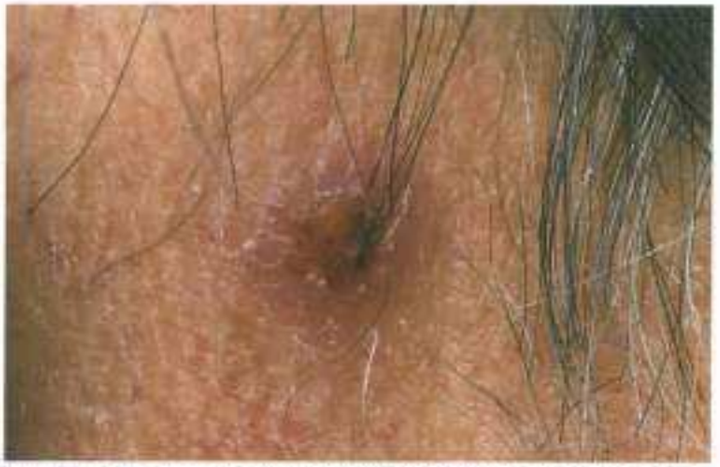


Fig. 17.64 Histoplasmosis. A single nodule was present on the temple of this patient, who had had a liver transplant for liver failure following hepatitis C infection. The diagnosis was only made following skin biopsy.

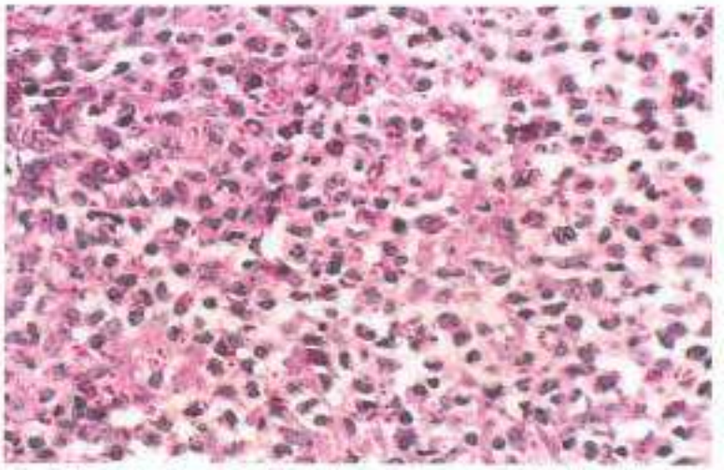


Fig. 17.65 Histoplasmosis. Intracellular yeasts are present (a distinguishing feature of this fungus). They are oval and bud. (Courtesy of Dr Jon Salisbury.)

Blastomycosis (Gilchrist's disease)

A chronic granulomatous suppurative disease, primarily of the lungs but occasionally disseminating to other areas including the skin caused by the fungus *Blastomyces dermatitidis*, in endemic areas.

Aetiology

The condition is seen in North America as far south as Mexico but is endemic in Mississippi and Kentucky. There is an African variety, which may be a different subtype, that is particularly common in Zimbabwe and often causes osteolytic bone lesions. The natural substrate for the fungus is probably wood debris or soil close to rivers. Human-to-human infection does not occur. It typically affects adult males in early middle age and results from inhalation of fungal conidia. *B. dermatitidis* is a budding yeast with a characteristic broad base. The local tissue reaction and subsequent course of the disease is determined by the immunological status of the patient. Pulmonary blastomycosis is very similar to tuberculosis and it may resolve or progress. Erythema nodosum may be associated. It may subsequently disseminate to other organs including the skin. There is a primary cutaneous form following trauma and introduction of the fungus into the skin, but this is usually seen in laboratory workers or pathologists.

Fig. 17.66 Blastomycosis. One yeast is shown with the characteristic broad base of the bud. (Courtesy of Dr Mary Moore.)

Clinical Features

Symptoms

There may be pulmonary symptoms in addition to skin lesions.

Morphology and distribution

- **Primary inoculation blastomycosis** A chancre followed 2 weeks later by lymphangiitis and lymphadenopathy.
- **Disseminated form** One or more papule or nodule, which may ulcerate and discharge pus usually on the trunk.
- **Pulmonary blastomycosis** Erythema nodosum may be associated with pulmonary infection.

Management

The diagnosis may be made by finding the quite thick-walled, rounded, spherical yeasts with broad-based buds in potassium hydroxide preparations of pus or skin scrapings (Fig. 17.66). *B. dermatitidis* may be grown on culture and there are serological tests and nucleic acid probes that may be used to identify specific ribosomal RNA sequences. Although traditionally amphotericin has been the treatment of choice, itraconazole is also effective and can be given orally and may supercede amphotericin.

Coccidioidomycosis

Coccidioidomycosis is a respiratory infection with the dimorphic soil fungus *Coccidioides immitis*, which may progress and disseminate.

Aetiology

C. immitis is found in the soil in the southern USA, northern Mexico, Argentina and Paraguay. Fungus-laden dust particles are inhaled by humans and domestic and wild animals. There are varied clinical manifestations including an acute form known as San Joaquin Valley fever, a primary pulmonary form and an uncommon disseminated variety. The last develops either rapidly by haematogenous spread of the spores or insidiously from a prior pulmonary lesion, particularly in the immunosuppressed, Filipinos, pregnant women in the third trimester and African-Americans. It affects all organs including the skin. Meningitis is common and mortality high. Silent infections as judged by positive skin tests are very common indeed, including in visitors to the endemic areas.

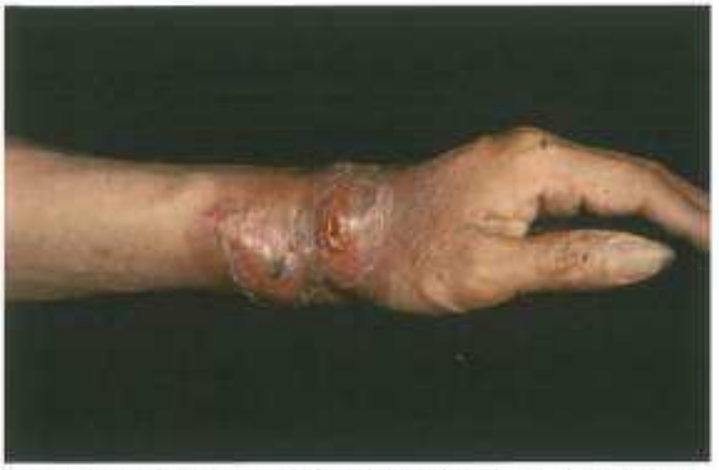


Fig. 17.67 Coccidioidomycosis. Several abscesses with multiple draining sites are present at the wrist. (Courtesy of the Institute of Dermatology.)

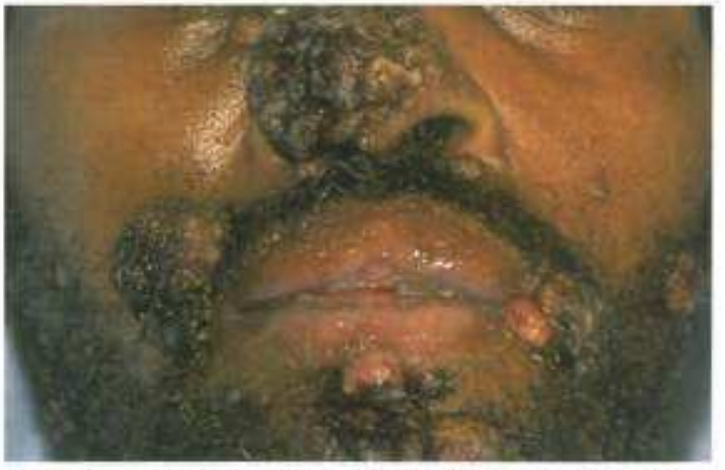


Fig. 17.68 Coccidioidomycosis. Multiple verucous granulomatous nodules develop in disseminated disease. (Courtesy of Dr Victor Newcomer, Santa Monica.)

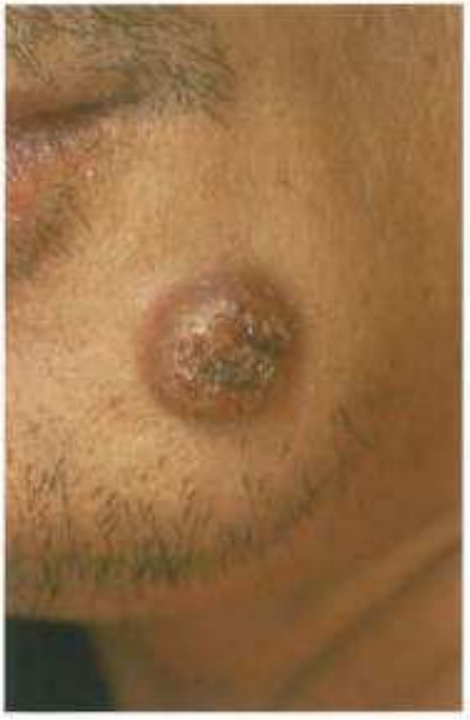


Fig. 17.69 Coccidioidomycosis. A warty nodule is present. (Courtesy of Dr Victor Newcomer, Santa Monica.)

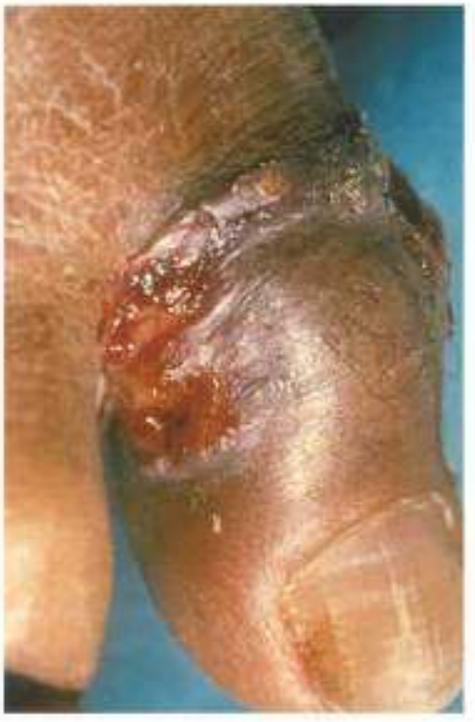


Fig. 17.70 Coccidioidomycosis. Multiple sinuses are draining through the skin secondary to bone involvement. (Courtesy of Dr Victor Newcomer, Santa Monica.)

Clinical Features

- **Disseminated form** The bone, meninges, subcutaneous tissues and skin may be involved. The skin lesions consist of grouped macules and papules, cellulitis, abscess (Fig. 17.67) formation, nodular verrucous granulomas (Figs 17.68 and 17.69), multiple sinus-draining tracts (Fig. 17.70) and ulcers.
- **Primary pulmonary form** Asymptomatic but may simulate tuberculosis. Erythema nodosum and erythema multiforme may occur.
- **Valley fever** There is an influenza-like illness composed of fever, chills, malaise, anorexia, aching, pruritic chest pain with cough, dyspnoea and occasionally blood-streaked sputum, night sweats and weight loss, accompanied by erythema nodosum

Management

The clinical manifestations are so diverse that the history of residence in or travel through an endemic area may suggest the diagnosis. Spherules may be found in potassium hydroxide preparations of sputum, cerebrospinal fluid or pus from the skin lesions. The fungus may be isolated on culture within 3 or 4 days on standard media. Skin biopsy is helpful. There is pseudoepitheliomatous hyperplasia with a diffuse, suppurative, granulomatous mixed dermal infiltrate in which there are large (10–80 μm) thick-walled spores with a granular cytoplasm (Fig. 17.71). DNA probes and serological complement fixation tests for *Coccidioides* antibodies are now much more time efficient. In the pulmonary form of the disease, rest is the preferred treatment. In disseminated disease, intravenous amphotericin has been the treatment of choice. Itraconazole, ketoconazole and fluconazole are now being used, although meningeal and joint infections do not respond well.

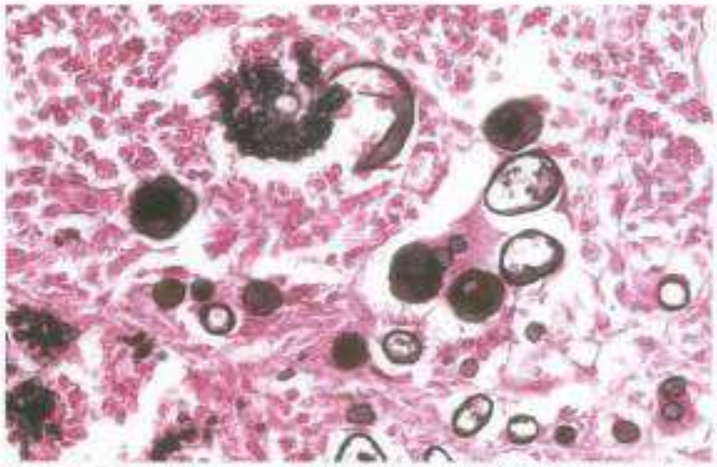


Fig. 17.71 Coccidioidomycosis. Spherules are present. One is seen releasing endospores. It is highly infectious and category 3 laboratory conditions are required. (Courtesy of Dr Mary Moore, Institute of Dermatology.)

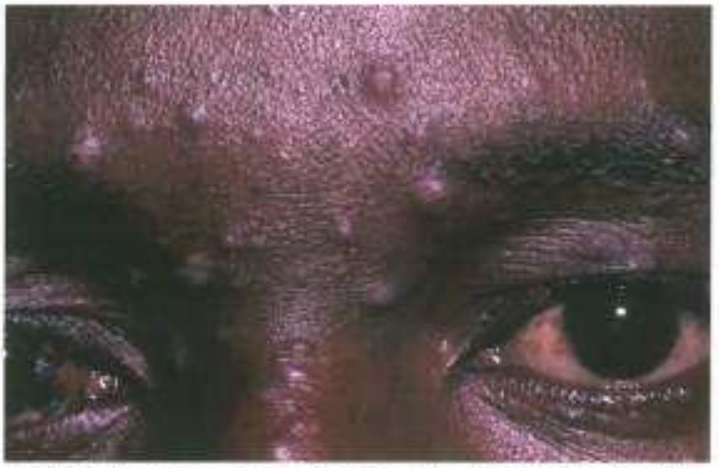


Fig. 17.72 Cryptococcosis. Papules and pustules may occur on the face. The diagnosis may be made by a skin biopsy. (Courtesy of Dr Barbara Leppard.)

Cryptococcosis

Cryptococcosis is an opportunistic infection with an encapsulated yeast, *Cryptococcus neoformans*, acquired through inhalation which particularly causes a meningoencephalitis but may affect the lungs, skin and other organs, especially in the immunosuppressed.

Aetiology

C. neoformans is ubiquitous and occurs worldwide. It is a non-mycelial budding yeast with a large mucinous capsule. Pigeon and other bird excreta are the commonest sources, but the soil, wood products and contaminated fruit and milk are others. It enters via the respiratory tract, but although pulmonary disease may occur, it is an unusual fungus in its predilection for the brain and the meninges. The skin may be involved and other organs such as the kidney and bone. It is more common in lymphomas, following organ transplantation and in AIDS.

Clinical Features

Symptoms

Not diagnostic but skin lesions in the context of immunosuppression might suggest the diagnosis.

Morphology and distribution

There is wide manifestation of clinical features, which include cellulitis and erythema nodosum-like swellings on the limbs, papules and pustules around the mouth and face (Fig. 17.72), plaques, nodules (Fig. 17.73), vesicles and ulcers.

Management

The large (5–15 μm) budding cells with their characteristic capsules may be seen in Indian ink preparation, Tzank smears or Gram stains of cerebral spinal fluid or pus and in histopathological specimens (Fig. 17.74). It may be cultured but cycloheximide inhibits its growth and should be omitted from the culture plate. Intravenous amphotericin is the treatment of choice with or without flucytosine. It is difficult to eradicate in AIDS and fluconazole is given to prevent relapse.

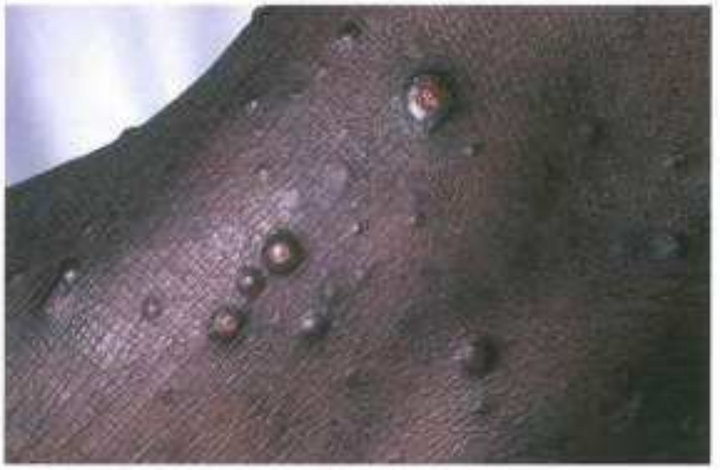


Fig. 17.73 Cryptococcosis. There are many papules and nodules present. It is caused by *Cryptococcus neoformans*, which enters via the respiratory tract but has a predilection for the brain and sometimes the skin, especially in the immunosuppressed. (Courtesy of Dr Barbara Leppard.)

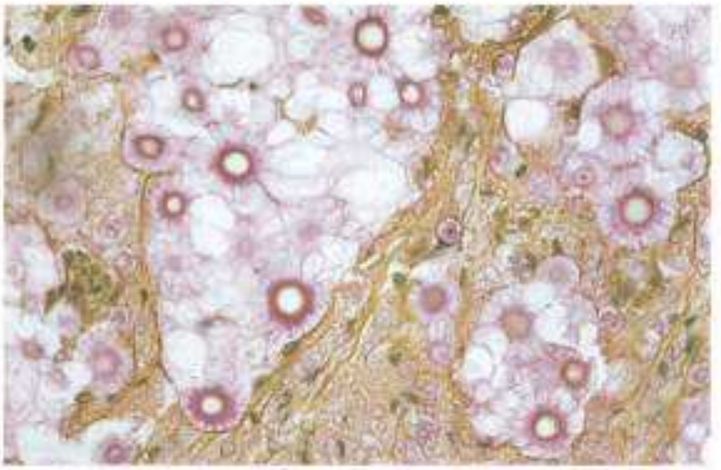


Fig. 17.74 Cryptococcosis. Striate radiations are visible caused by contraction of the gelatinous capsule of the large budding cells. This is a mucicarmine stain. (Courtesy of Dr Mary Moore, Institute of Dermatology.)

Tumbu fly infection

A parasitic infection of the skin and musosa by larvae of *Diptera* (true flies) giving rise to a red oedematous swelling, resulting from larval invasion of the tissues (myiasis).

Aetiology

Myiasis is the invasion of human tissues by the larvae of a fly species. The tumbu fly, *Cordylobia anthropophaga*, is widespread in humid subtropical and tropical Africa. The eggs are deposited on moist clothing and blankets and sandy soil. They can survive a fortnight. The larvae penetrate the skin (usually thighs or buttocks), where they mature before emerging and continuing their life cycle on the ground. *Dermatobia hominis* is the other fly to cause a pimary cutaneous infection. Female flies lay their eggs on the abdomen of blood-sucking insects (e.g. mosquito). When these feed on exposed skin, the warmth of the skin stimulates the attached eggs to hatch, producing larvae which penetrate the skin and result in a furuncular lesion. The condition is seen particularly in children in rural communities. Rodents, cattle, horses and pigs represent reservoir hosts. The eggs may also be deposited in neglected wounds and ulcers or accidentally ingested in contaminated food or drink (intestinal myiasis). The eyes, ears and urogenital tract may also be infected.

Clinical Features

The larvae produce a red oedematous boil-like swelling after penetration of the intact skin. Intermittent slight movement may be detected. Their respiratory tubules may be seen poking through it.

Management

The maggots (Fig. 17.75) rise to the surface if occluded with petroleum jelly. This is the standard treatment.

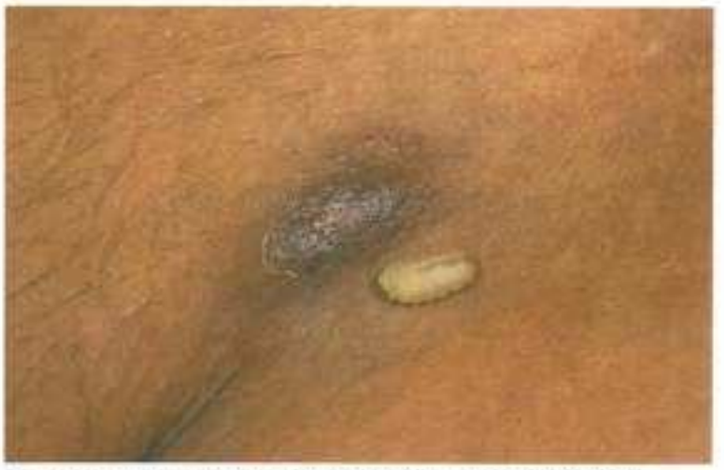


Fig. 17.75 Tumbu fly. A maggot is present having just emerged from the adjacent furuncular lesion.

Tungiasis (Jiggers)

A self-limiting ectoparasitic infection caused by penetration of female sand fleas (*Tunga penetrans*) into the epidermis.

Aetiology

Tungiasis thrives in warm dry sandy soil, viz. deserts, beaches and around pigsties and stables. It is seasonal, being common in the dry season in underdeveloped rural and urban slum communities. It has spread form Latin America to Angola via sand from travellers from Brazil and on to sub-Saharan Africa, East Africa and Madagascar. It occurs in adults. It is rare in children. The animal reservoir occurs in dogs, cats and rats. The gravid female, which is 1 mm in length and is the smallest blood-sucking flea, burrows at an angle of 45–50° into the soft skin of the feet and produces a tiny red papule after about three hours. After 24 hours the abdominal segment enlarges and the parasite is visible as an itchy painful nodule with a central black dot. It reaches its maximum size after 4 days and there is a white painful pearly lesion with a central opening from which the enlarged flea excretes faeces and eggs. As it involutes, the remains of the parasite form a crust and subsequently scar. The flea may transmit tetanus.

Clinical Features

Symptoms

After initial 'sting' of penetration, there may be pain as the flea enlarges.

Morphology

Single or multiple white, grey or yellow papules with a small brown-black central opening, which emits a serosanguinous exudate (Figs 17.76 and 17.77). White specks (eggs) may be seen on the skin.

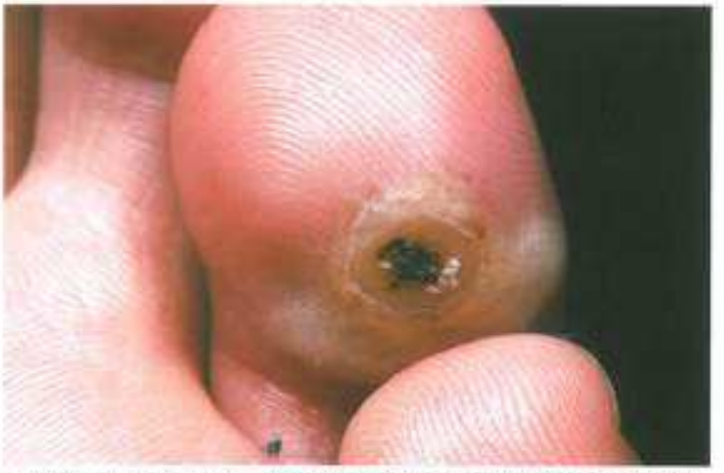


Fig. 17.76 Tungiasis (Jiggers). There are single or multiple white-grey papules with a small brown-black central opening.

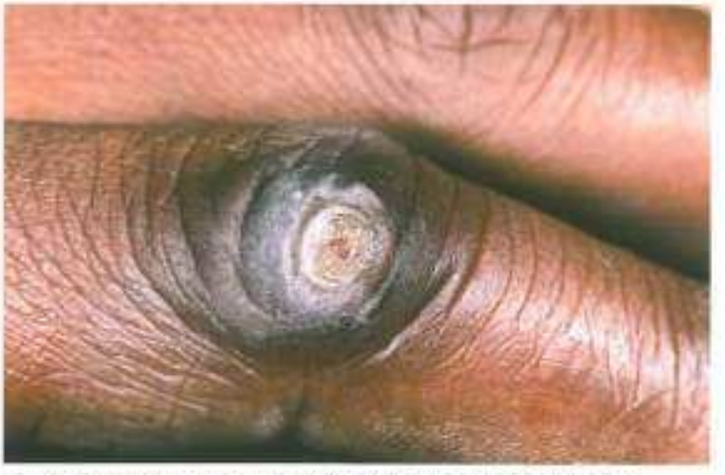


Fig. 17.77 Tungiasis (Jiggers). This is a self-limiting infection caused by penetration of female sandflies (*Tunga penetrans*) into the epidermis.

Distribution

Subungual, interdigital and along the medial borders of the feet.

Management

Sepsis is common in neglected cases with abscess formation, lymphangiitis, lymphoedema and tissue necrosis. Surgical extraction, antibodies and antitetanus injections are the mainstay of treatment.

Reactive disorders of the skin and adverse drug reactions

18

There are various recognizable cutaneous patterns, which occur in response to noxious agents, which may or may not be identifiable. These include toxic erythema, erythema multiforme, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilic and systemic symptoms (DRESS), fixed drug eruptions, urticaria, vasculitis and erythema nodosum. These and reactions to sunlight are described here.

Toxic erythema

A generalized, red, macular or maculopapular (morbilliform) skin eruption.

Aetiology

A common abnormal cutaneous pattern. It may have a number of causes.

Drugs

Although immunological (especially delayed type hypersensitivity) mechanisms are probably responsible, these morbilliform drug reactions do not always recur with rechallenge. There are no routine laboratory tests to determine which drug is responsible. Patch tests and lymphocyte transformation tests have mixed results. Any drug may produce a toxic erythema, but the most frequent offenders are:

- **Antibiotics.** Penicillin derivatives (such as ampicillin, amoxicillin and flucloxacillin), sulphonamides (particularly septrin) and cephalosporins (Fig. 18.1). The rash appears several days (classically 10) after commencing treatment, often after it is finished, which confuses the patient and sometimes the doctor. Ampicillin is the commonest cause, with about 10% of the population reacting in this manner, which increases to 100% in patients with infectious mononucleosis (Fig. 18.2), and ampicillin should be avoided if that diagnosis is suspected. If it is inadvertently represcribed when the patient has recovered from glandular fever, a second attack of toxic erythema will probably not develop. However, the drug should be avoided for life. Females and older patients, especially if taking many drugs and those with AIDS and lymphatic leukaemia are at risk.
- **Barbiturates.**
- **Non-steroidal anti-inflammatory drugs.**
- **Anticonvulsants.**
- **Allopurinol.**
- **Radiotherapy.**

Bacteria

The eruptions of scarlet fever or the toxic shock syndrome are forms of toxic erythemas. The former is produced by a streptococcal erythrotoxin and the latter by a staphylococcal pyrogenic exotoxin, but the accompanying general symptoms and signs will lead to the correct diagnosis.

Viral infections

The exanthematic and morbilliform eruptions of rubella and measles are specific erythemas where the evolution, morphology, distribution, systemic symptoms and signs allow the diagnosis to be made. However, non-specific toxic erythemas occur that are presumed to be viral because of the general clinical picture and pyrexia. Coxsackie, Epstein–Barr, adeno-, entero- and echoviruses, HIV and HHV 6 are most often implicated in these cases.

TOXIC ERYTHEMA OF THE NEWBORN (ERYTHEMA TOXICUM NEONATORUM)

Toxic erythema of the newborn is a very common rash that occurs within 48 hours of birth. A blotchy, macular erythema occurs on the face, trunk (Fig. 18.3) and proximal parts of the limbs and clears within 2 days. There is no systemic upset and the cause is not known.

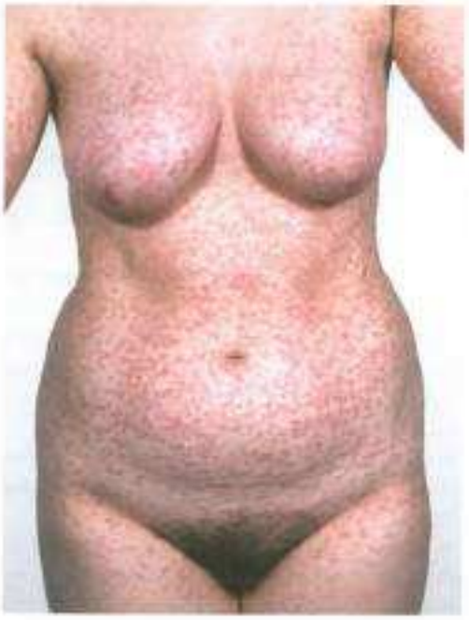


Fig. 18.1 Toxic erythema. The eruption is widespread, erythematous and often papular. Drugs, in this case ampicillin, are commonly responsible for these morbilliform patterns.

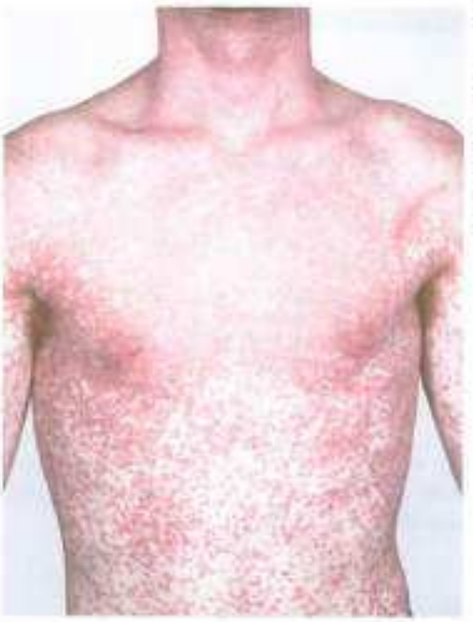


Fig. 18.2 Amoxicillin and infectious mononucleosis. All patients who are prescribed ampicillin or amoxicillin for the sore throat associated with glandular fever will develop a toxic erythema.

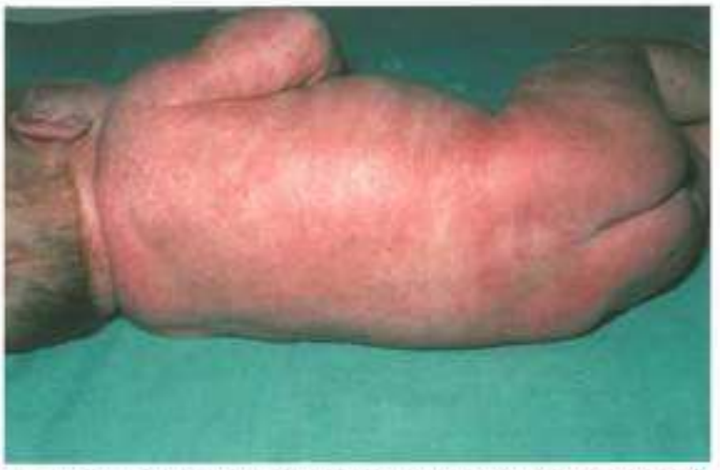


Fig. 18.3 Toxic erythema of the newborn. This is a common evanescent 'toxic' erythema of unknown cause that occurs in the first days after birth and involves the face, trunk and limbs.

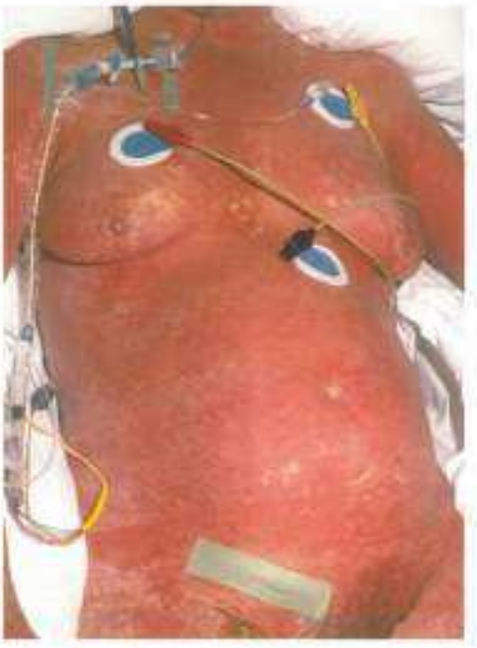


Fig. 18.4 Toxic erythema. This patient is erythrodermic. It may be difficult to discern which drug is responsible for the reaction, because the patient may be taking multiple agents.

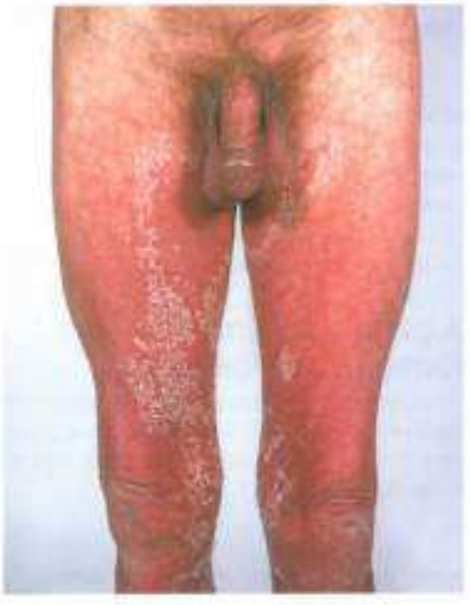


Fig. 18.5 Toxic erythema. There is widespread erythema followed by desquamation. (Courtesy of St Mary's Hospital.)

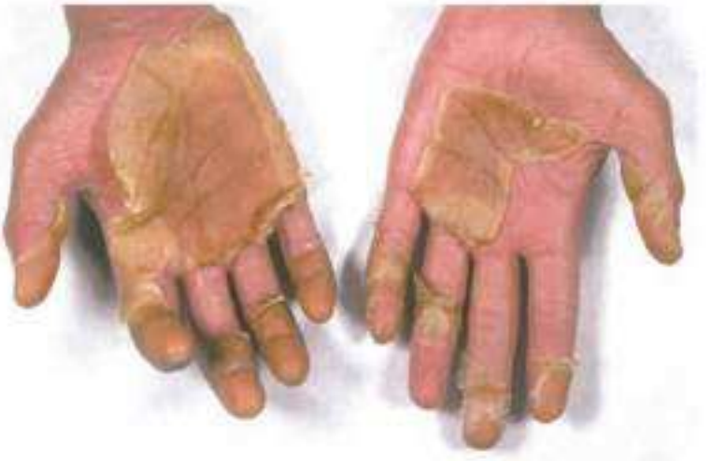


Fig. 18.6 Toxic erythema. Marked shedding (desquamation) of the palmar and plantar skin occurred after this patient had taken an overdose of barbiturates.

Idiopathic

In many, the cause is obscure and the patient is otherwise perfectly well. The eruption clears within a week.

Clinical Features

Symptoms

The eruption is usually itchy if caused by a drug, and asymptomatic if from an infection. Fever accompanies the latter, and specific symptoms and signs may indicate the source of the infection.

Morphology

Red macules appear, which may become papular and merge into one another, producing a blotchy erythema. Erythroderma may result (Fig. 18.4). Desquamation follows (Figs 18.5 and 18.6).

Distribution

Practically all the body surface is affected.

Management

Management depends on the diagnosis. Bacterial infections and viral infections are treated appropriately. Drug eruptions are managed as follows:

- The drug should be discontinued immediately to avoid further erythroderma, but if the drug is essential, it is permissible to 'treat through' the rash, only discontinuing the medication if the rash deteriorates.
- The patient should be reassured that the eruption will clear within 8 to 10 days, but not immediately.
- Prompt relief of the irritation, which is often considerable, may be achieved by the use of:
  - calamine, with or without 1–2% menthol; this is one of the helpful uses of calamine (it is often used indiscriminately for itchy eruptions and only serves to mask the physical signs and hinder diagnosis)
  - systemic antihistamines, which are of symptomatic value
  - systemic steroids occasionally are required, either as a single injection of tetracosactrin in depot form, or as oral prednisolone, starting at 30 mg daily and reducing by 5 mg every third day
- If the condition occurs in hospital, the family practitioner should be informed and the allergy recorded prominently on the notes.
- It is wise for a patient to wear a 'Medic-Alert' thereafter.

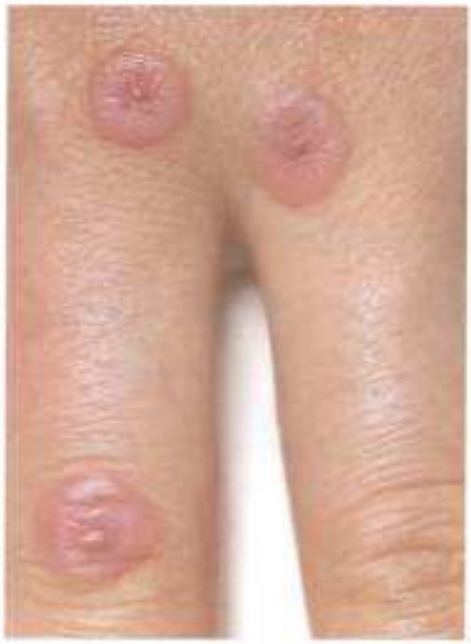


Fig. 18.7 Erythema multiforme. The central area of the lesion is more involved than the periphery so that it appears like a target. (Courtesy of St Mary's Hospital.)

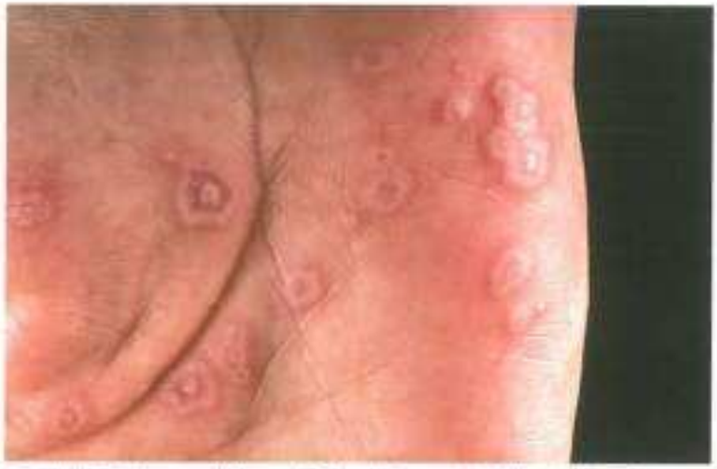


Fig. 18.8 Erythema multiforme. Palmar involvement with target lesions is classical. It is invariably caused by herpes simplex but other viruses such as orf may also be responsible. It lasts about 3 weeks.

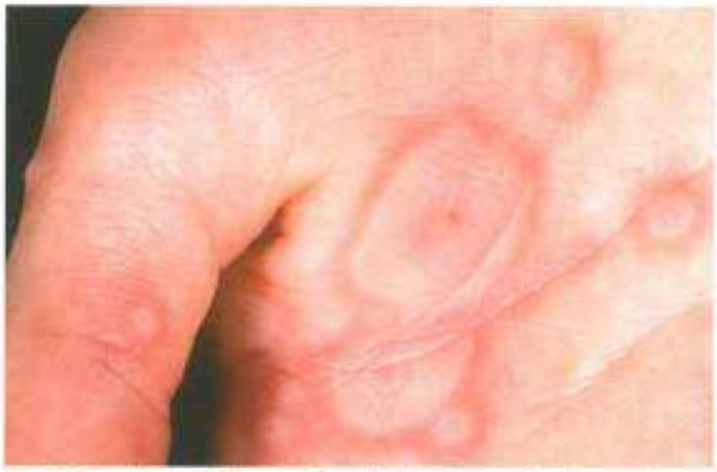


Fig. 18.9 Erythema multiforme. The vesiculo-bullous type is an intermediate between the iris type and the Stevens–Johnson/toxic epidermal necrolysis form. The target arrangement is still visible.

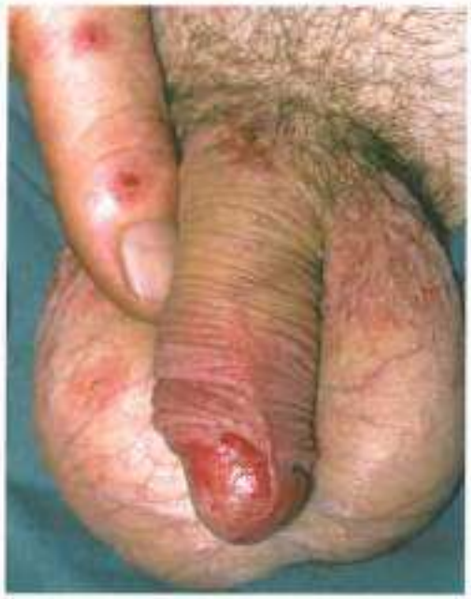


Fig. 18.10 Erythema multiforme. The genitalia are often involved. Erosions are present. Target lesions may be seen on the patient's finger.

Erythema multiforme

A distinctive self-limiting mucocutaneous pattern of acrally located target-like lesions, usually secondary to herpes simplex but occasionally to other infections.

Aetiology

Described by von Hebra and known as erythema iris or papulatum, some confusion resulted because atypical forms and the Stevens–Johnson syndrome were included under the title erythema multiforme. These are now described with toxic epidermal necrolysis, which is useful because these are mainly caused by drugs whereas the target form of erythema multiforme is usually caused by herpes simplex. Other viruses (vaccinia, infectious mononucleosis, orf and hepatitis B), *Mycoplasma pneumoniae* and histoplasmosis may produce a similar picture. Herpes simplex DNA has been detected in the cutaneous lesions of erythema multiforme using in situ hybridization studies and the polymerase chain reaction (PCR).

Clinical Features

Symptoms

An asymptomatic acral rash, often following a cold sore.

Morphology

- **Iris type (erythema multiforme minor)** The lesions are red or purple and annular. The central area is slightly raised, cyanotic (Fig. 18.7) and more involved than the periphery, probably because the central area has borne the brunt of the vascular damage (Fig. 18.8). This configuration resembles a target.
- **Vesiculo-bullous type (erythema multiforme major)** This is an intermediate between the simple iris type and the Stevens–Johnson syndrome. The degree of damage to the skin is greater and the centre of the target lesion becomes a vesicle or bulla with less marked changes around the periphery (Fig. 18.9). As the blisters break, raw, painful erosions and ulcers result, particularly in the mouth and on the nose and genitalia (Fig. 18.10).

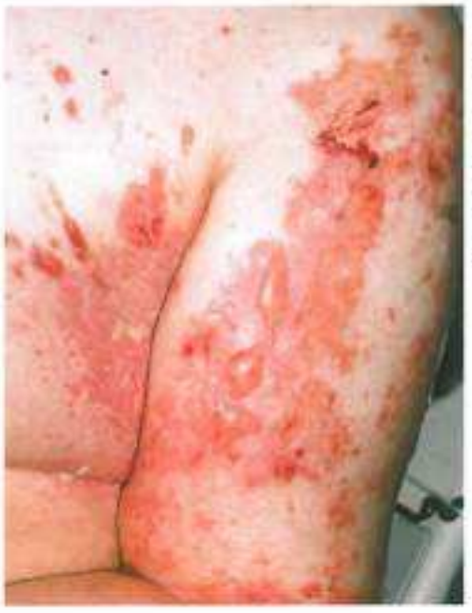


Fig. 18.11 Stevens–Johnson syndrome. The lesions are vesiculo-bullous and more widespread and the mucous membranes are involved. It may be confused with bullous pemphigoid, but immunofluorescence is negative.

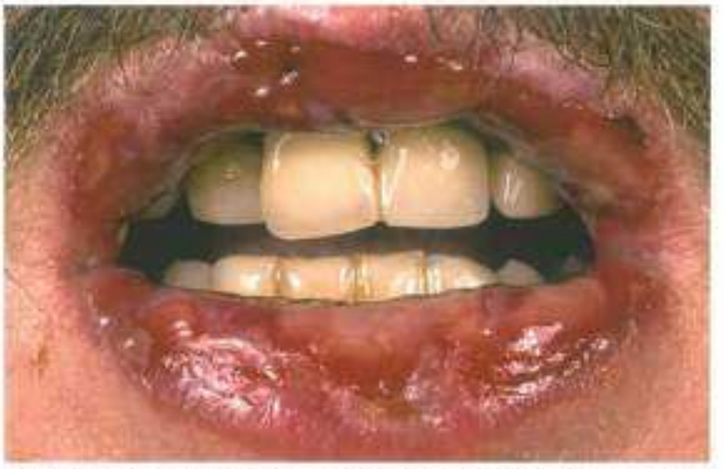


Fig. 18.12 Erythema multiforme. The mouth and lips are involved in the iris and Stevens–Johnson types.

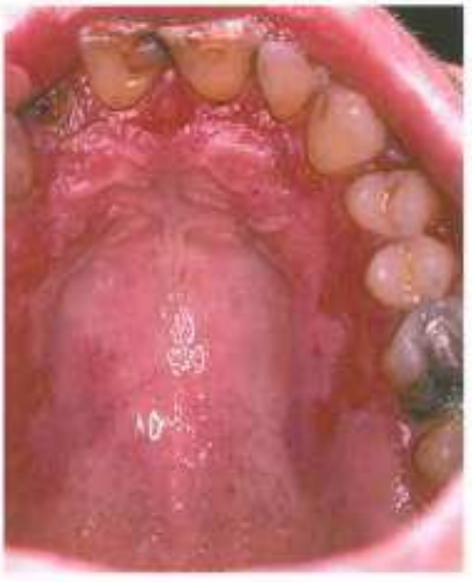


Fig. 18.13 Erythema multiforme. There are considerable erosions and denudation of the oral mucosa. Swabs should be taken to culture for herpes simplex.

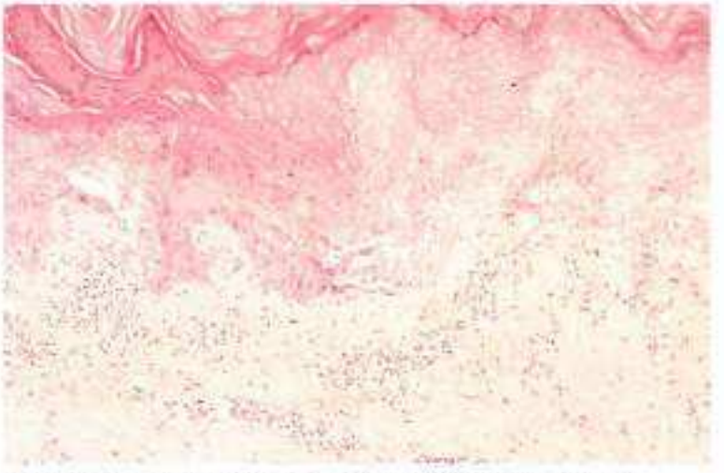


Fig. 18.14 Erythema multiforme. In this example, there is total necrosis (infarction) of the epidermis on the right with underlying vesiculation. A predominantly lymphocytic infiltrate is present in the superficial dermis. On the left, numerous cytoid bodies are seen.

Distribution

The lesions are symmetrical and occur on the extremities, particularly on the palms, backs of the hands, forearms, dorsa of the feet, soles and lower legs. They are more widespread in the vesiculo-bullous type (Fig. 18.11) and the mucous membranes are involved (Figs 18.12 and 18.13).

Management

The common iris type is unmistakeable, but the blistering type may be confused with bullous pemphigoid, and a skin biopsy for histology and immunofluorescence is invaluable. Immunofluorescence is positive in bullous pemphigoid but not in erythema multiforme. Histologically, there is vasodilatation and oedema in the upper dermis, with a lymphohistiocytic infiltrate surrounding the blood vessels, which is most prominent in the region of the dermo-epidermal junction. Epidermal necrosis is often present, either as scattered individual cells or else involving the entire thickness (Fig. 18.14). Degeneration of basal keratinocytes may result in dermo-epidermal separation with subsequent vesiculation.

There are two variants:

- **Recurrent erythema multiforme** Some patients have several attacks a year and the condition persists for decades. In less than half a cause is found and half of these are due to *H. simplex*. The rest have been attributed to hepatitis C, mycoplasma, recurrent vulvovaginal candidiasis, menses or a drug (e.g. acetaminophen). Treatment is unsatisfactory. Prolonged antiviral agents, dapsone, IVIG (intravenous immunoglobulin) and azathioprine are amongst the standard remedies.
- **Persistent erythema multiforme** This is rare. There are uninterrupted, often papulonecrotic or bullous mucocutaneous lesions, which may be associated with EBV, HSV, inflammatory bowel disease or neoplasia.

Ordinary erythema multiforme is treated symptomatically or with a short course of systemic steroids.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

SJS and TEN represent a spectrum of severe drug-induced mucocutaneous changes ranging from a severe, flaccid, bullous eruption of the skin and mucous membranes to an acutely painful separation (sheeting) off of the skin and extensive epidermal death.

Aetiology

In 1956 Lyell described four cases of 'a scalded skin syndrome' that subsequently turned out to be three different entities. One was a condition caused by a staphylococcal exotoxin, which occurs in children, now known as the staphylococcal scalded skin syndrome. The second was a generalized bullous fixed drug eruption, which is always reproducible although the patient sometimes denies drug usage. The third, toxic epidermal necrolysis, is described here. It is a severe drug eruption with features of the Stevens–Johnson syndrome. Lyell's patient was taking phenylbutazone.

Stevens–Johnson syndrome and toxic epidermal necrolysis represent a spectrum of disease that is quite distinct from erythema multiforme. Stevens–Johnson syndrome may be considered to have less than 10% and toxic epidermal necrolysis greater than 30% detachment of the skin. Although it is usually an idiosyncratic reaction to a drug, it is reproducible for a short while only. A co-factor, for example HIV or influenza leads to these syndromes. Other drugs include carbamazepine, allopurinol, phenylbutazone, sulphonamides, barbiturates, cytostatic agents, radiotherapy, thiazides, furosemide and occasionally vaccines (measles, mumps and rubella) and mycoplasma pneumonia.

There is acute skin failure and major metabolic abnormalities in TEN. It is mediated by cytotoxic (CD8 positive) T cells causing apoptosis, a rapid immunologically silent (i.e. it does not trigger an inflammatory response) cell death mediated through a death receptor pathway, particularly Fas. The Fas-Fas ligand pathway activates intracellular capsases, which lead to the cell death. Genetic factors are relevant with a strong association for example between HLA-B 1502 and carbamazepine-induced TEN. The elderly with reduced renal clearance are particularly at risk.

Clinical Features

Symptoms

The syndrome is often heralded by fever, sore throat, cough and burning eyes for 1–3 days. The onset is acute. The eyes, nose and genitalia may be involved before the skin, which is tender.

Morphology

Poorly defined, erythematous macules with darker purpuric centres become confluent, followed by flaccid bullae (Fig. 18.15) that sheet off the skin leaving a red, raw, oozing eroded surface (Fig. 18.16), very similar to a burn.

Distribution

The whole integument may be involved (Fig. 18.17) with accentuation in the flexures. Blistering and ulceration in the mouth may make it impossible to eat.

Systemic features

There is fever and systemic toxicity with inflammation of the gastrointestinal (causing haemorrhage) and respiratory tracts (causing dyspnoea, hypoxia and tachypnoea) and eyes (causing purulent conjunctivitis, synechiae, corneal ulceration, xerophthalmia, symblepharon and blindness). There may be sepsis, multiorgan failure and pulmonary embolism. Anaemia, neutropenia (which augurs badly) and lymphopenia are common. Overall mortality is 30%. Healing is slow and strictures may result (especially in the genitalia). The scalp is not affected.

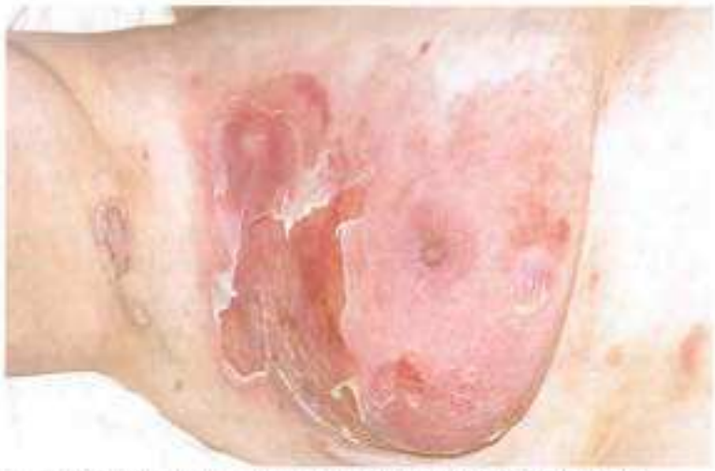


Fig. 18.15 Toxic epidermal necrolysis. There is 'sheeting' of the skin, to leave a raw, denuded area. This was secondary to a barbiturate. (Courtesy of Dr R. Staughton, Chelsea and Westminster Hospital.)

Fig. 18.16 Toxic epidermal necrolysis. The epidermis of the flaccid bullae sheet off, leaving a red raw oozing eroded surface, which is very painful.

Fig. 18.17 Toxic epidermal necrolysis. There is sheeting away of the epidermis revealing raw denuded skin. This is the most serious form of drug eruption with a high mortality.

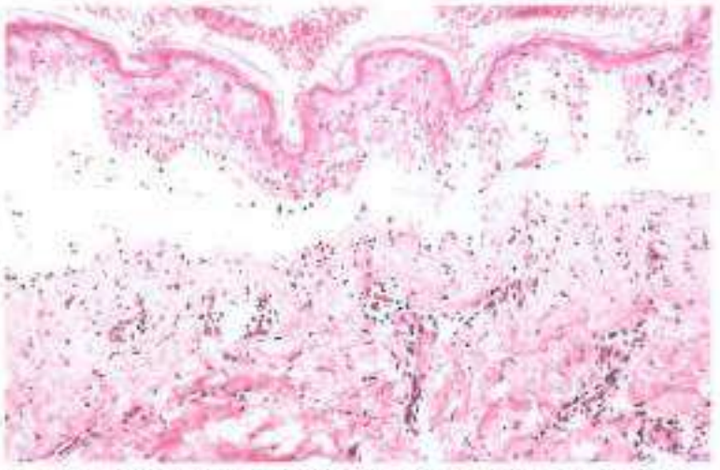


Fig. 18.18 Toxic epidermal necrolysis. A subepidermal blister is evident. The overlying keratinocytes are necrotic. Note the retention of the dermal papillary outline. A very slight chronic inflammatory cell infiltrate is present.

Management

The blistering and sheeting of the skin revealing raw painful erosions is characteristic, but immunobullous disorders can easily be excluded by performing immunofluorescence. The histology reveals blistering or sloughing of the epidermis through damage to the basal cell layer arising with epidermal necrosis. Inflammation is often slight (Fig. 18.18).

Prompt diagnosis and withdrawal of the drug may reduce mortality, particularly with drugs having short half-lives.

Pain control, non-stick sheets, air mattresses, nasogastric feeding, catheterization, peripheral venous access, eye care, pulmonary toilet and prophylactic antibiotics are essential.

SCORTEN is a mathematical prognostic model based on seven variables: (i) age >40, (ii) presence of malignancy, (iii) tachycardia, (iv) BSA >10%, (v) urea >10, (vi) glucose >14, (vii) bicarbonate >20, where prognosis for 0–1 is (3.2%), 2 (12%), 3 (35%), 4 (58%) and >5 (90%).

Intravenous immunoglobulins should be given immediately to forestall apoptosis. The use of pulse systemic steroids is controversial. Plasmapheresis may aid the removal of the drug and its metabolites. Granulocyte colony-stimulating factors may improve the neutropenia.

Annular erythema

Annular erythema is a term used to describe the appearance of one or several erythematous rings on the skin. There are four clinical types. The margin of the ring is red and very slightly raised, while the central area heals and looks quite normal (Fig. 18.19). There is usually no surface change. However, a fine, thin line of scale does occur towards the edge of the erythema in *erythema annulare centrifugum* and the annular erythema occurs in waves, with concentric scaling bands like the grain in wood, in *erythema gyratum repens*. In most cases, no cause can be found for an annular erythema but occasionally it may be associated with malignancy, particularly blood dyscrasias (Fig. 18.20) and dysproteinaemias. Erythema gyratum repens is indicative of malignancy. Other forms of erythema include *erythema chronicum migrans* (Ch. 13), secondary to the tick bite that causes Lyme disease, and *erythema marginatum*, which occurs in rheumatic fever and Still's disease. Obviously, ringworm is annular and red but it has a characteristic palpable and scaly margin and the fungus is easily demonstrated under a microscope.

ERYTHEMA ANNULARE CENTRIFUGUM

A chronic figurate erythema with a distinctive pathology.

Aetiology

The cause is usually obscure, but is occasionally secondary to a haematological malignancy, ascariasis, candidiasis or severe tinea pedis.

Clinical Features

Symptoms

The red rings are relatively asymptomatic.

Morphology

Each individual lesion begins as a red oedematous papule, which enlarges peripherally to form an annular, arcuate or polycyclic pattern (Fig. 18.21). Quite large rings are formed with central clearing (Fig. 18.22). The more superficial forms of the disorder have a peripheral scale. In deeper forms, the edge is palpable without scaling. Individual lesions usually disappear within a few weeks, but fresh ones arise.

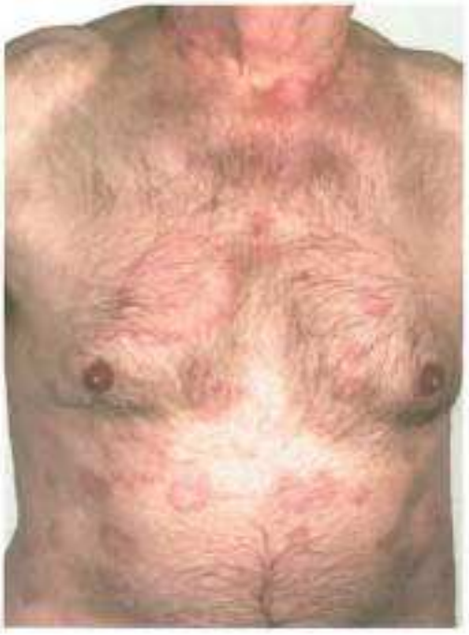


Fig. 18.19 Annular erythema. There are one or several erythematous rings. The margin is red and slightly raised while the centre looks quite normal. The cause is often obscure.

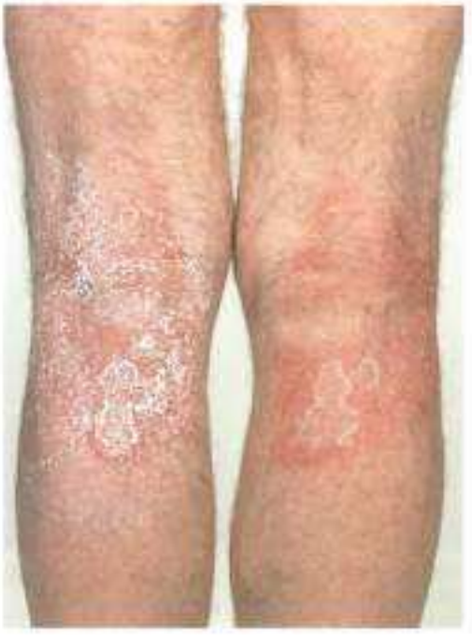


Fig. 18.20 Annular erythema. This man had annular, red, scaly lesions on his limbs. A full blood examination revealed that he had hairy cell leukaemia, and this was the cause of the annular erythema.

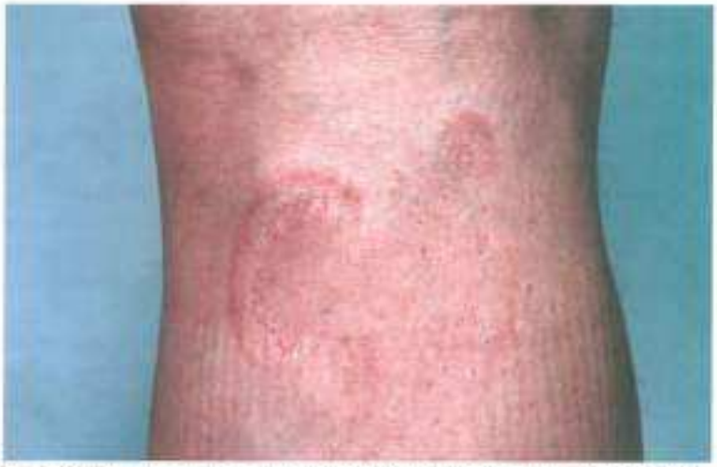


Fig. 18.21 Annular erythema. The edge of the lesion is quite characteristic with a raised red margin with a fine line of scale adjacent to it, forming arcuate or linear arrangements.

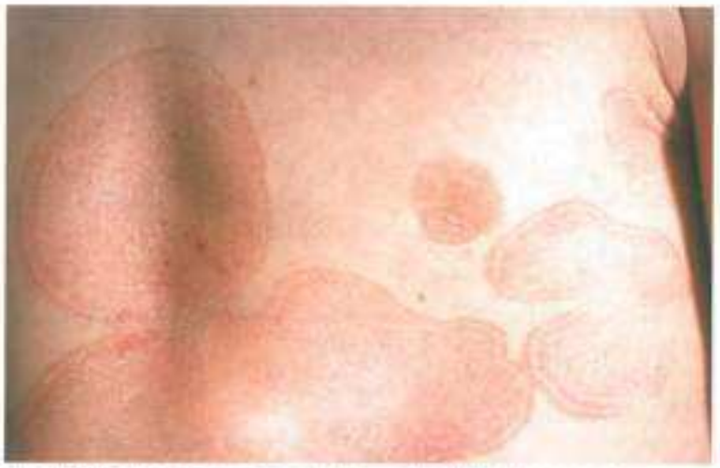


Fig. 18.22 Erythema annulare centrifugum. In addition to the annular erythema there is a fine, thin, scaly line towards the edge of the lesion. The cause is unknown. (Courtesy of St Mary's Hospital.)

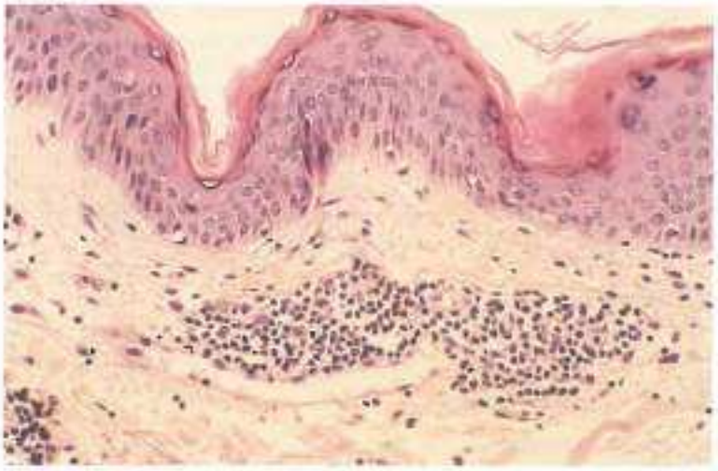


Fig. 18.23 Erythema annulare centrifugum. A heavy infiltrate of lymphocytes surrounds the superficial vasculature.

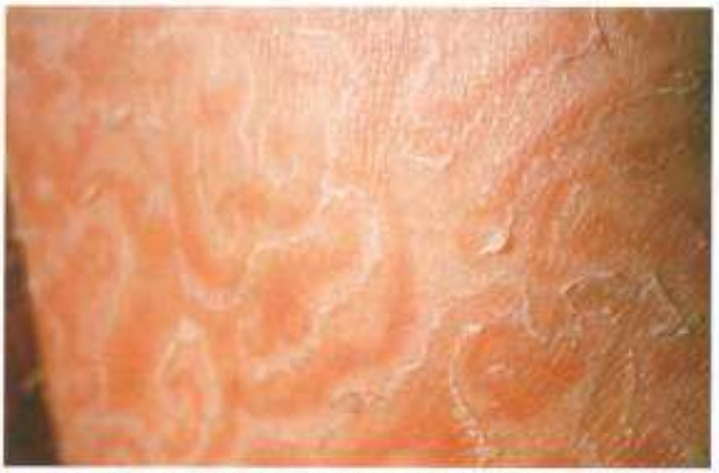


Fig. 18.24 Erythema gyratum repens. The scale resembles the grain in wood. (Courtesy of the Institute of Dermatology.)

Distribution
The lesions are most common on the buttocks, thighs and upper arms.

Management
The histology shows a characteristic dense perivascular lymphocytic sleeving of the vessels of the upper and mid-dermis (Fig. 18.23). If no cause is found, there is no specific treatment, but topical steroids can sometimes help.

ERYTHEMA GYRATUM REPENS
A rare paraneoplastic characterized by regular waves of annular erythema that spread over the body.

Aetiology
Almost all cases are associated with internal malignancy, particularly carcinoma of the lung, breast, stomach, bladder and prostate, and may represent a cross-reaction between tumour antigens and the skin.

Clinical Features
Symptoms
The lesions occur in bizarre concentric rapidly migrating bands that follow one another in repeated waves.

Morphology
There is a scale to be seen towards the periphery of each ring, which resembles the grain in wood (Fig. 18.24). Fresh waves of erythema may appear within existing rings.

Distribution
The lesions cover most of the body.

Management
The diagnosis is a clinical one. The histology is similar to that of other annular erythemas and it is imperative to search for an underlying malignancy. The eruption is reversible if the malignancy is treated.

ERYTHEMA MARGINATUM RHEUMATICUM
A transient annular erythema associated with rheumatic fever and Still's disease.

Aetiology
The condition occurs in Still's disease and in about 10% of patients with active rheumatic fever (carditis, migratory polyarthritis and chorea). It is an immune reaction to a Lancefield group A streptococcal pharyngitis. A more persistent annular erythema occurs in adult rheumatoid arthritis (sometimes known as adult Still's disease).

Clinical Features

The eruption is easily missed. It is transient, most prominent in the afternoons and symptomless.

Morphology

The lesions consist of recurrent crops of different sizes of red rings. The edge of the eruption may be flat or just palpable. There is central pallor. The rings are discrete and are round or polycyclic.

Distribution

Lesions occur particularly on the trunk (especially the abdomen) but also on the buttocks and less often on the limbs.

Management

The diagnosis is clinical, but the histology may reveal a neutrophil-rich perivascular infiltrate. Other investigations are those for rheumatic fever and rheumatoid arthritis.

Urticaria and angio-oedema

Urticaria and angio-oedema are transient, itchy, red swellings of the skin and mucous membranes secondary to the release of histamine and other vasoactive agents from granules within the mast cells near blood vessels.

Aetiology

Histologically, there is vasodilatation, dermal oedema and a mild perivascular infiltrate of lymphocytes and eosinophils. In angio-edema, the deep dermis and subcutaneous tissues are involved.

Mast cells may degranulate as a result of the following mechanisms:

- **Direct stimulation** Certain drugs (for example morphine, codeine, ethanol, polymyxin B) and some bacterial, plant or invertebrate toxins directly stimulate the mast cells to degranulate.
- **Immediate hypersensitivity** This immediate or accelerated form of hypersensitivity results from the reaction between the antigen (drugs, serum injections, penicillins in dairy products, foods and inhaled allergens) and IgE molecules fixed to sensitized tissue mast cells in the skin, respiratory tract, gastrointestinal tract or cardiovascular system, or to circulating basophils. Consequently, bronchospasm, laryngeal oedema and anaphylactic shock may accompany urticaria. The reaction occurs within minutes or up to 36 hours after exposure. Penicillin is the most common cause.
- **Immune complex disorders** Urticaria may accompany *serum sickness*, which is characterized by fever, lymphadenopathy, myalgia, arthralgia, nephritis, neuritis, hepatitis and hypocomplementaemia. The reaction occurs 4–12 days after exposure to heterologous serum (although blood, plasma, immunoglobulin fractions and drugs are more common causes). The antigen has to remain in the circulation long enough to encounter the antibody (IgG or IgM) once it has been synthesized so that circulating antigen–antibody complexes can be formed.
- **Anaphylotoxins C3a and C5a stimulation** These are derived from the classical and alternative pathway of complement and may also act upon mast cells. Mast cell degranulation is inhibited by agents that raise intracellular cyclic adenosine monophosphate (cyclic AMP) and stimulated by those that raise cyclic guanosine monophosphate (cyclic GMP).

Clinical Features

Symptoms

The patient describes itchy blotches, blisters or wheals that disappear after a few hours. There may be no physical signs when the patient is examined, but the history is usually typical enough for the diagnosis to be made anyway.

Morphology

The lesions may be annular (Fig. 18.25), vary in size and shape (Fig. 18.26) and are raised and smooth with no surface scale or change (Figs 18.27 and 18.28). They are red peripherally, with a tendency to central pallor, are short lived and fade without trace.

Distribution

They can occur anywhere but especially where clothes are tight, such as under a waistband. In angio-oedema, they may occur around the eyes, on the lips, genitalia and hands.

Systemic features

If the angio-oedema affects the tongue and larynx, the disorder becomes life threatening, because of the possibility of asphyxia. Anaphylaxis and circulatory collapse may then result.

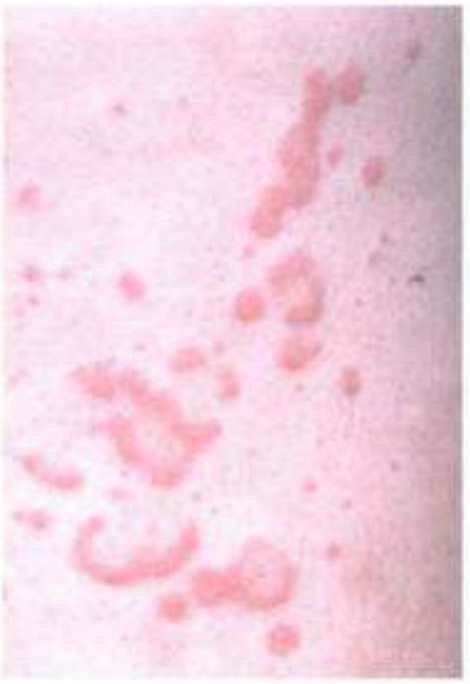


Fig. 18.25 Urticaria. The lesions are pink swellings with a tendency to central pallor. They are very itchy.

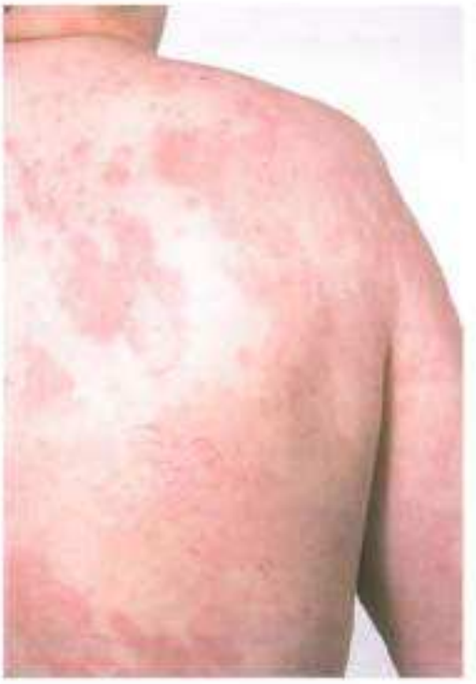


Fig. 18.26 Urticaria. Each wheal is transient, lasting less than 24 hours and disappears without trace. They occur anywhere on the body.

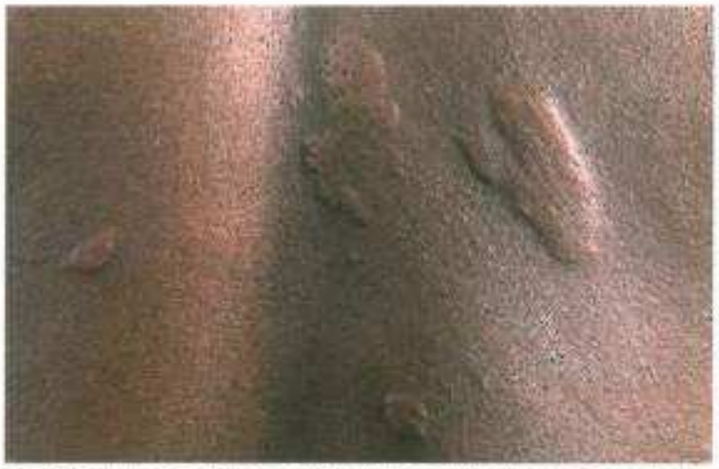


Fig. 18.27 Urticaria. There are swellings with no surface change. The erythema may be difficult to discern in black skin although it is visible here.

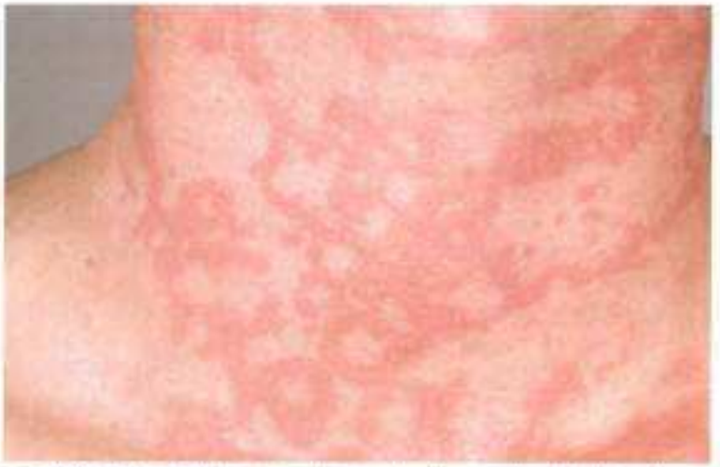


Fig. 18.28 Urticaria. Itchy erythematous oedematous swellings that last a few hours and disappear without trace are known as wheals. It is known colloquially as 'hives' or 'nettle rash'.

Types of Urticaria

Urticaria is a physical sign. There are a number of possible causes.

Acute urticaria

Acute urticaria is the most satisfactory type to explain. Each time the allergen is ingested, the condition reappears and is thus reproducible, but challenge is inadvisable because of the danger of anaphylaxis.

The most common causes are:

- **Drugs (allergic)** Penicillin, cephalosporins, aspirin, toxoids, animal sera, polypeptide hormones (e.g. insulin), quinidine.
- **Drugs (histamine liberators)** Morphine, codeine, radiocontrast media.
- **Foods** Fish, nuts, eggs, chocolates, shellfish, tomatoes, pork, strawberries, milk, cheese, spices and yeast, dyes and additives (benzoates and tartrazine).
- **Infection** Focal sepsis (e.g. urinary tract), viral (e.g. hepatitis), *Candida*, protozoa, toxocariasis.
- **General** Lupus erythematosus, lymphoma, polycythaemia, macroglobulinaemia.
- **Latex** Gloves, medical equipment.

When a food is implicated, there is sometimes an associated gastrointestinal upset. The most common foods involved are shellfish, strawberries or mushrooms. Adverse reactions to radiocontrast media present as angio-oedema/urticaria, often in association with hypotension. This is probably caused by the direct release of histamine from mast cells and represents an idiosyncratic sensitivity. The urticarial reaction to latex rubber gloves is usually obvious to the wearer of the gloves, but patients are at risk because they may be touched by medical staff wearing gloves or be exposed to medical equipment containing latex and in this situation the diagnosis may not be so obvious. Infection (e.g. the prodrome of hepatitis), focal sepsis (e.g. urinary tract infection) and helminths may cause urticaria. Urticaria requires a thorough history and examination to elucidate a cause.

Physical urticarias

Physical urticarias are common. The diagnosis can be made from the history.

- **Dermographism** The patient notes that the skin irritates, and linear wheals (Fig. 18.29) appear as a result of scratching or direct pressure. It is an exaggerated response of the skin to trauma that results in the release of histamine and other vasoactive agents from mast cells. The patients, who are often young adults, may have ordinary urticaria as well. The condition is demonstrable by drawing a line on the skin. The tendency to dermographism may take months or years to disappear. Antihistamines are of limited benefit.

Fig. 18.29 Dermographism. This is an exaggerated response of the skin to trauma, which is common in young adults. It may persist for years before disappearing spontaneously.

- **Pressure urticaria** Although rare on its own, it does occur to a minor extent in many patients with urticaria. The swellings occur after prolonged pressure, for example on the buttocks after sitting or on the soles of the feet after standing for a long time. The lesions are itchy, may be painful and last several hours. It does not respond well to antihistamines but eventually goes into remission.
- **Solar, cold and heat urticarias** These conditions are rare. The wheals can be reproduced with the use of solar-simulating equipment, ice cubes or a test tube of hot water, depending on the physical entity involved.

Solar urticaria is a rare, occasionally incapacitating chronic IgE-mediated photodermatosis of children and young adults, characterized by the development of a wheal and flare and sometimes anaphylaxis within minutes of photoexposure. Type I is an abnormal serum or dermal chromophore which is activated to become a photoallergen against which the IgE antibodies are directed. In type II there are circulating IgE antibodies against a normal chromophore. Paradoxically, irradiation may induce tolerance and prevent the eruption.

Patients with cold urticaria must be warned against bathing in cold water as this may produce a massive transudation of fluid into the skin, with

hypotension, syncope and anaphylactic shock. Drinking cold water may produce swelling of the lips, tongue and pharynx. The condition is acquired in adolescence and is usually self-limiting.

- **Aquagenic urticaria** This is common. Patients note small itchy wheals that last 10–15 minutes after exposure to water, particularly after a bath or shower. The temperature of the water does not modify the response. It is rather a tiresome complaint that may persist for many years and some patients are quite frustrated by it. There is really no satisfactory treatment. It is occasionally a presenting symptom of polycythaemia rubra vera or myelodysplastic syndrome.
- **Cholinergic urticaria** This is a common condition in youth. The lesions are intensely pruritic, red wheals, less than 2 mm in diameter (Fig. 18.30), that develop in response to sweating, exercise, emotion and hot foods. It is postulated that an increase in blood temperature triggers a neural reflex which releases acetylcholine from sympathetic nerve endings. Acetylcholine increases intracellular cyclic GMP, so activating the mast cells to degranulate. Attacks last only a few minutes. The condition ultimately resolves. Prophylactic antihistamines are not particularly effective.

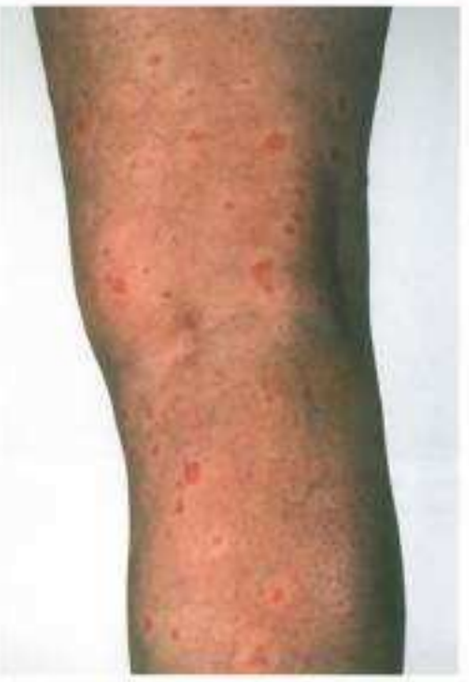


Fig. 18.30 Cholinergic urticaria. Very small, short-lived red wheals occur in young people, precipitated by such stimuli as exercise, emotion or sweating. Note the perilesional blanching of the skin.

Chronic non-allergic urticaria

Chronic non-allergic urticaria is defined as an urticaria that lasts longer than 6 weeks for which no cause can be found. The wheals occur sometimes on a daily basis or less frequently. Ultimately it disappears, sometimes to return years later. The patient is otherwise well. Most, however, are atopics or have a family history of eczema, asthma, hay fever or indeed urticaria. Most have circulating IgG autoantibodies against IgE or its receptor and are able to release histamine. Some not only get urticaria but also angio-oedema and may have a concomitant physical urticaria, including pressure urticaria.

Distinctive urticarial syndromes

- **Cryopyrin-associated periodic syndromes** (CAPS) are inherited autoinflammatory disorders of innate immunity characterized by flu-like symptoms, recurrent fevers, increased cytokine expression and episodic inflammation with end organ damage including renal amyloidosis, accompanied by urticaria. They include *Muckle–Wells syndrome* (MWS), *Familial cold autoinflammatory syndrome* (FCAS) and *Neonatal onset multisystem inflammatory disorder* (NOMID), a spectrum of disease caused by a mutation in the CIAS1 (synonym NALP3) gene on chromosome 1q44, which encodes cryopyrin and results in upregulated production of interleukin-1β. Muckle–Wells syndrome is inherited as an autosomal dominant or arises de novo. There are recurrent burning itchy urticarial plaques lasting 48 hours in response to cold. It begins just after birth and is associated with fever, headache, malaise and leucocytosis. Progressive sensorineural deafness and amyloid may result. These heredofamilial syndromes do not respond to antihistamines but the recombinant human Il-1 receptor antagonist anakinra and canakinumab, a fully human anti IL-1β monoclonal antibody which selectively block IL-1β are major therapeutic advances. FCAS is an autosomal dominant mutation in the NLRP3 gene on chromosome 1q44. There is early onset cold-induced urticaria with chills, fevers, arthralgias, myalgias, headache and conjunctivitis.
- **Familial Mediterranean fever** is an autosomal recessive disorder of Sephardic Jews, Armenians and Arabs associated with intermittent erysipelas-like erythemas at acral sites, atypical (non-pruritic) urticarial eruptions associated with cold and air conditioning, fever, peritonitis, pleurisy or synovitis. It may eventuate in renal amyloidosis, but is now entirely controllable by the serendipidous finding that colchicine is effective.
- **Urticarial vasculitis** is a clinicopathological entity of urticarial lesions, which last longer than 24 hours and have evidence of leucocytoclastic vasculitis. 50% of patients have synovial involvement (arthralgias and occasionally arthritis). Most cases are idiopathic and ultimately resolve, but a hypocomplementaemic urticarial vasculitis or venulitis syndrome (HUVS) with extracutaneous involvement of the synovia and sometimes renal and respiratory tracts is well recognized. It is classically associated with serum sickness. In HUVS there are anti C1q antibodies, which cause a reduction in complement, C3, C4 and C1q, but the C1 esterase is normal. Other causes of urticarial vasculitis include:
  - certain connective tissue disorders, e.g. SLE and Sjögren's
  - haematological conditions, e.g. chronic lymphatic leukaemia and non-Hodgkin's lymphoma
  - drugs, especially non-steroidal anti-inflammatory.
- **Schnitzler's syndrome** This is a chronic neutrophilic urticarial condition with recurrent fevers and painful osteosclerotic bone lesions associated with a raised ESR and IgM gammopathy, Waldenström's and marginal zone lymphoma.
- **Weil's syndrome** This is a rare recurrent granulomatous dermatitis with eosinophilia, with features of urticaria (Fig. 18.31) and cellulitis that

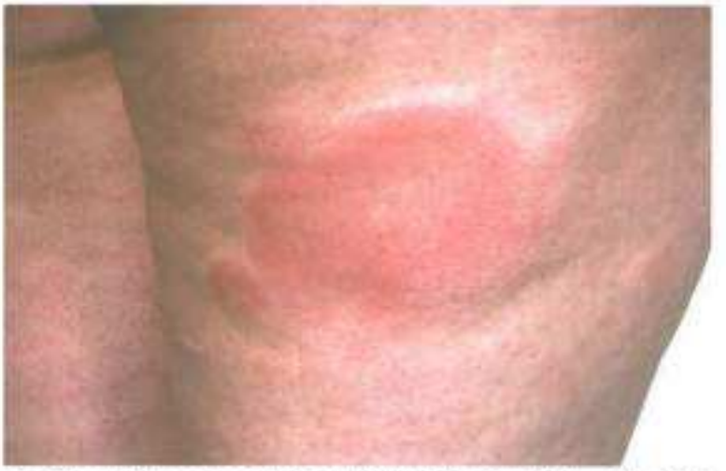


Fig. 18.31 Weil's syndrome. There are itchy red plaques with features of urticaria and cellulitis that resolve with a green coloration; it is occasionally associated with fever and haematological disorders.

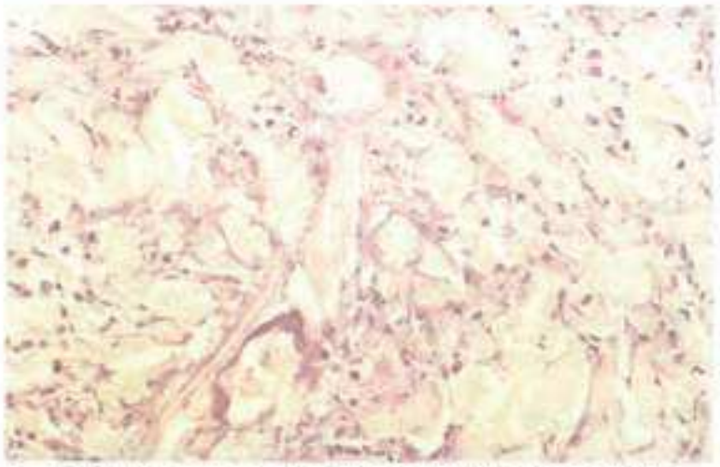


Fig. 18.32 Well's syndrome. There is tissue eosinophilia, oedema and flame figures. The cause is unknown.

resolve without scarring but producing a green colour with a characteristic histology of oedema, tissue eosinophilia and flame figures (Fig. 18.32).

- **Eosinophilic dermatoses** Eosinophils are leucocytes with a distinctive cytoplasm containing granules, which stain red with eosin, an acidic dye. Eosinophilic infiltrates are frequently found in urticaria and in association with parasitic infections, arthropod bites, drug eruptions, eczema, granuloma faciale, Well's syndrome, Churg–Strauss disease and bullous pemphigoid (an important diagnostic clue in the prebullous phase).
- **Hypereosinophilic syndromes** (HES) are characterized by a marked eosinophilia (> 1500/mcl). At present they are classified into myeloproliferative and lymphocytic. The former affects males, is rare, and causes prolonged eosinophilia and organ damage. There is mucosal ulceration, fever, fatigue, weight loss, splenomegaly, endomyocardial fibrosis, cardiomyopathy and a raised serum B12 tryptase level. There is a mutation in the FIP1L1-PDGFRA fusion gene on 4q12 with a tyrosine kinase product, which transforms haematopoietic cells (into myelomonocytic leukaemia with eosinophilia or chronic eosinophilic leukaemia with evolution to acute myeloid leukaemia or T lineage lymphoblastic lymphoma) and is over 100 times more sensitive to the inhibitory effects of imatinib than is the BCR-ABL kinase of patients with chronic myeloid leukaemia. Lymphocytic HES is characterized by severe pruritus, dermatitis, erythroderma, urticaria/angio-oedema, lymphadenopathy and very occasionally endomyocardial fibrosis. It may evolve into lymphoma.

Angio-oedema

Angio-oedema (Figs 18.33 and 18.34) may accompany urticaria in about half of the patients. However, sometimes patients will just have infrequent attacks of angio-oedema. It is important in these patients to exclude hereditary or acquired angio-oedema by checking C1 inhibitor and C4 levels and also relevant drugs such as captopril. Patients with acquired depletion of the esterase inhibitor of the first component of complement may have an associated lymphoproliferative disorder, serum sickness or a cutaneous necrotizing venulitis (sometimes known as atypical erythema multiforme or lupus erythematosus-like syndrome).

Management

In acute cases of urticaria, the cause may be readily determined. The urticarial eruptions associated with serum sickness, lupus erythematosus or the prodrome of serum hepatitis are more persistent than true urticaria and, histologically, are actually a leucocytoclastic vasculitis. They, therefore, differ from the urticarias under discussion. In chronic urticaria, which is arbitrarily defined as attacks that last longer than 2 months, a specific cause is rarely elucidated but it is believed to be an autoimmune disorder.

The history is important. The patient usually has identified the cause in acute urticaria, in which case it should be withdrawn. The physical and chronic urticarias too have a characteristic history. Investigations are rather unrewarding. Blood tests, such as a full blood count, erythrocyte sedimentation rate (ESR), antinuclear factor and SMAC, are usually normal. Skin-prick and radioallergosorbent tests (RAST) are often positive in a non-specific way as part of an atopic diathesis (that is, pollen and animal fur positivity), but elimination of the allergens elicited usually makes little difference. Biopsy may be useful to rule out an urticarial vasculitis or Well's syndrome.

In chronic urticaria, it is often wise to ask the patient to make a list of the things ingested 24 hours prior to each attack, in an attempt to identify a pattern of precipitants. An elimination diet free from preservatives, under the guidance of a dietitian, may be worth trying.

Prophylactic antihistamines are the mainstay of treatment and are effective. With the older antihistamines, the limiting factor was the hypnotic

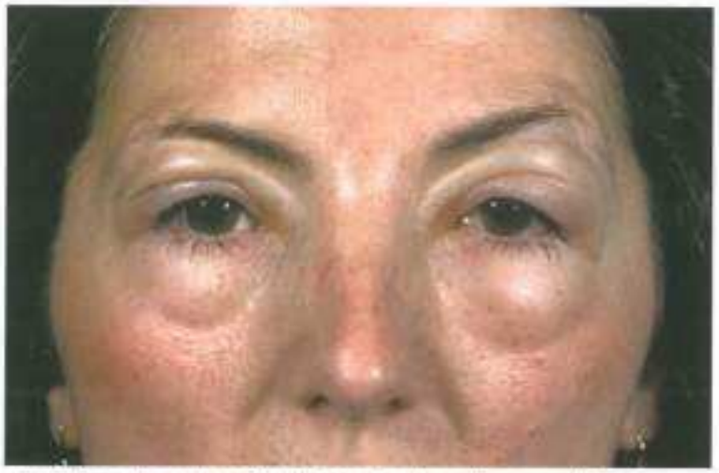


Fig. 18.33 Angio-oedema. There is considerable swelling around the eyes. (Courtesy of Dr M. Clement.)

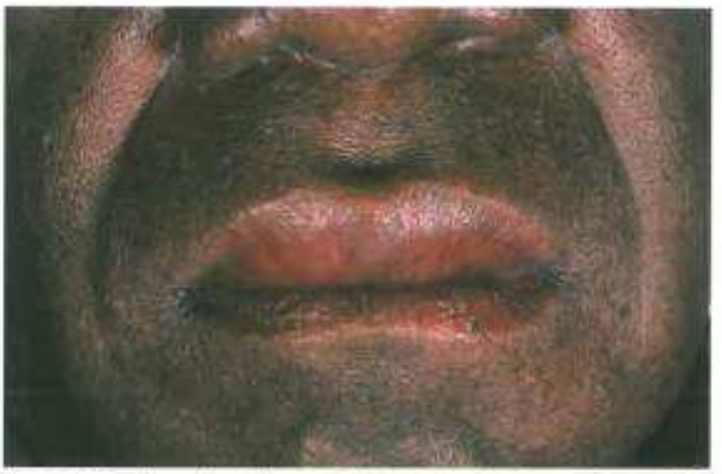


Fig. 18.34 Angio-oedema. The upper lip is grossly swollen in comparison with his lower. The danger here is of laryngeal oedema asphyxia and anaphylactic shock.

effect, however this can be used to effect at night with hydroxyzine hydrochloride, which also has an anxiolytic effect. It is sometimes quite sedative so the patient has a hangover effect the next morning, consequently, it is wise to start at 10 mg and increase by 20 to 30 mg at night if the patient can tolerate it. The non-hypnotic antihistamines such as terfenadine, astemizole and cetirizine have been a major advance. They should be taken in the amount that controls the symptom. This appears to be a safe approach with most antihistamines, although arrhythmias have been described with some of the newer antihistamines when given in higher doses. It is important to take the drugs regularly and prophylactically to control the disease rather than taking them at the time of the attack. They should be taken until the disorder has cleared completely and then tailed off, watching carefully for recurrence of symptoms. Other treatments include intravenous immunoglobulins, and immunosuppressive agents including azathioprine, methotrexate or ciclosporin to suppress the autoimmune phenomenon.

Aquagenic urticaria is sometimes relieved by taking propranolol, 10 mg, half an hour before a bath. Baking soda added to the bath is also helpful.

Occasionally admission to hospital is beneficial. It affords an opportunity to study the effects of elimination diets, allows the patient to rest, and is particularly useful if psychogenic factors are present. These do not cause the disease, but undoubtedly some patients become very distressed, disproportionately to the degree of their affliction. This is sometimes because there are other factors in their lives that are frustrating them and making the urticaria worse. Management of these sources of unhappiness will be of benefit, coupled with encouragement and prophylactic antihistamines.

Anaphylaxis

In anaphylaxis, epinephrine (adrenaline) 1:1000 is required. It is given either subcutaneously in a dose of 0.5–10 ml, or intravenously as 0.1 ml over a period of 1 minute. Resuscitation equipment is necessary, including an airway, oxygen, suction apparatus and equipment for tracheotomy. Other drugs that may be given are injectable antihistamines, such as chlorphenamine (chlorpheniramine) and systemic steroids, hydrocortisone hemisuccinate, intravenously or intramuscularly. Aminophylline may be necessary.

Patients may be taught self-management for angio-oedema. Many inject epinephrine (adrenaline) and EpiPen auto-injectors are available. A 2% ephedrine spray may be used for oropharyngeal administration and medihalers are also available.

Hereditary angio-oedema

An autosomal dominant inherited deficiency of the inhibitor of the first component of complement that results in transient oedema of the skin and gastrointestinal and upper respiratory tract.

Aetiology

There are mutations in SERPING1 (serpin peptidase inhibitor clade G, member 1) on chromosome 1 causing quantitative (type 1) or qualitative (type 2) deficiency of complement C1 inhibitor leading to activation of the kallikrein-kinin, complement, fibrinolytic and coagulation systems, resulting in release of vasoactive plasma kinins. This results in transient and recurrent swelling of the skin, mucous membranes, gastrointestinal tract and larynx, which is associated with a significant mortality. It often begins in childhood but may occur later. Occasionally there is no familial history.

Clinical Features

Symptoms

The recurrent spontaneous episodes of transient oedema are quite different from ordinary urticaria. They do not itch and cover large areas.

Morphology

The oedema is non-pitting, circumscribed and lasts between 24 and 72 hours.

Distribution

Anywhere on the skin, especially the face and extremities.

Systemic features

Individual patients vary in the pattern of attacks: some have frequent and others only occasional episodes. It may affect primarily the skin or just the gastrointestinal tract. Oedema of the latter gives rise to symptoms of abdominal pain, vomiting and diarrhoea. There is a serious danger of asphyxiation from involvement of the larynx.

Management

The antigenic and functional activity of C1 INH is markedly decreased as are levels of C4. C1 and C3 are normal. C1 *is depressed in acquired C1 INH deficiency* (associated with SLE, paraproteinaemia and lymphoproliferative disease) and may be used to distinguish the two. Other family members should be investigated. The management of an acute attack is supportive, i.e. alleviation of airway obstruction and C1 INH concentrate or fresh frozen plasma. Inhibitors of plasminogen activation such as epsilon-aminocaproic acid and tranexamic acid are helpful to prevent attacks during surgery although both drugs have a high incidence of side-effects. Impeded androgens (i.e. those androgens with less virilizing potential) such as danazol, oxymetholone and stanozolol are extremely helpful in most patients with the disease. They stimulate C1 INH production. Their side-effects include hepatotoxicity, a disordered menstrual cycle and, in children, impairment of growth.

Purpura and vasculitis

Purpura is a physical sign and not a disease per se. The lesions are purple and, unlike erythema, do not blanch on pressure. Flat, purpuric lesions less than 1 cm in diameter are known as petechiae (Fig. 18.35). They occur mostly on the lower limbs; larger lesions are called ecchymoses or bruises (Figs 18.36 and 18.37). Purpura is caused by either a disorder of the blood or an abnormality of the blood vessels.

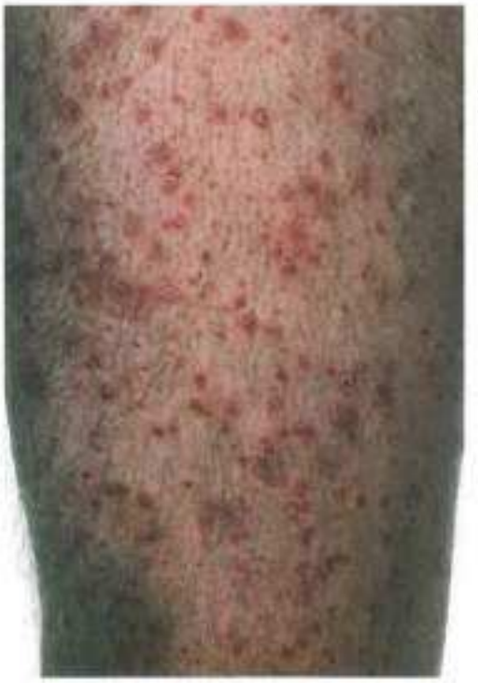


Fig. 18.35 Petechiae. Small purpuric macules that do not blanch on pressure are known as petechiae. The lower extremities are most commonly affected in thrombocytopenia.

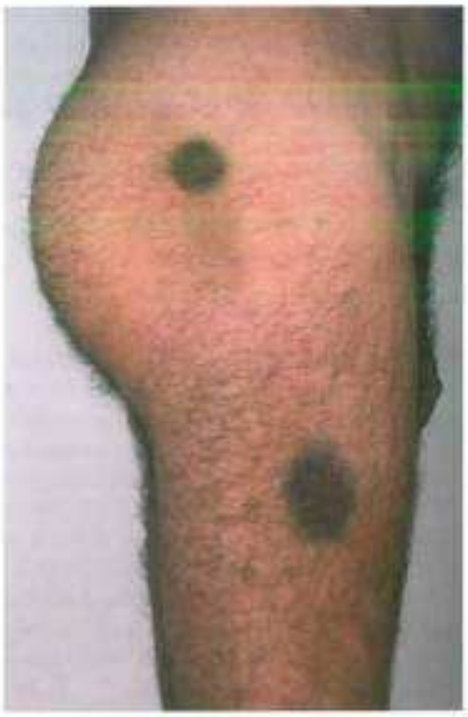


Fig. 18.36 Ecchymosis. Extensive bleeding into the skin causes ecchymoses (or bruising). The patient has haemophilia.

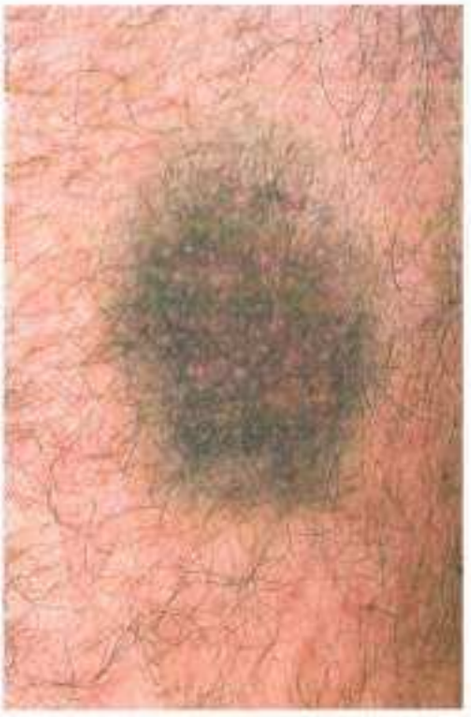


Fig. 18.37 Haemophilia. Large areas of bleeding into the skin occur. The purple and greenish discoloration so typical of bruising is seen.

Blood disorders include:

- Platelet abnormalities, viz.
  - idiopathic thrombocytopenic purpura
  - secondary thrombocytopenia
    - bone marrow infiltration (e.g. leukaemia or carcinomatosis)
    - bone marrow arrest (e.g. drugs or irradiation)
- Coagulation abnormalities (e.g. haemophilia)
- Plasma protein abnormalities (e.g. macroglobulinaemia)

Blood vessel defects include:

- Congenital defects of vessel walls (e.g. Ehlers–Danlos syndrome)
- Increased vascular permeability (e.g. scurvy)
- Fragility of vessel walls (e.g. solar or steroid)
- Damage to vessel walls (e.g. vasculitis or embolic)

As a general rule, non-inflammatory causes produce flat petechiae (e.g. thrombocytopenia or macroglobulinaemia) or ecchymoses (e.g. coagulation defects or solar purpura), whereas vasculitic or embolic disorders (Fig. 18.38) produce palpable purpuric lesions.

VASCULITIS

Whereas purpura is a prominent physical sign in vasculitis, the latter is a pathological term, the classification of which is confused. It has variously been based on clinical features, histology (the size of blood vessel involved and type of infiltrate in the vessel walls), the frequency of other organ involvement and various haematological, biochemical, serological and immunological abnormalities. Regrettably the correlation between them is often poor and some patients cannot be readily categorized.

Large vessels are involved in giant cell (*temporal arteritis*) and in Takayasu arteritis. The former is a disorder of the aorta and its branches and has a special predilection for the extracranial branches of the carotid artery, particularly the temporal artery and occurs in older patients particularly in association with polymyalgia rheumatica. *Takayasu's arteritis* is a granulomatous disorder of the aorta and its major branches and is seen in younger age groups. Although nodules or ulceration may occur over the temporal artery in temporal arteritis, the cutaneous aspects of these diseases are limited.

Polyarteritis nodosa is a necrotizing arteritis of medium-sized or small arteries. In *Kawasaki's disease*, large and small arteries may be involved, particularly the coronaries. In *Wegener's granulomatosis*, small and medium-sized vessels are involved with a necrotizing vasculitis which may involve the kidneys and skin and there is granulomatous inflammation in the respiratory tract. In the *Churg–Strauss syndrome* the necrotizing vasculitis also affects small and medium-sized vessels but there is an eosinophil-rich and granulomatous inflammation of the respiratory tract causing asthma associated with eosinophilia. *Microscopic polyangiitis* (polyarteritis) is a necrotizing vasculitis also affecting small and medium-sized arteries but without immune complex deposition but frequently associated with necrotizing glomerulonephritis and pulmonary capillaritis. *Leucocytoclastic angiitis* affects small vessels (the capillaries, venules or arterials), and is usually

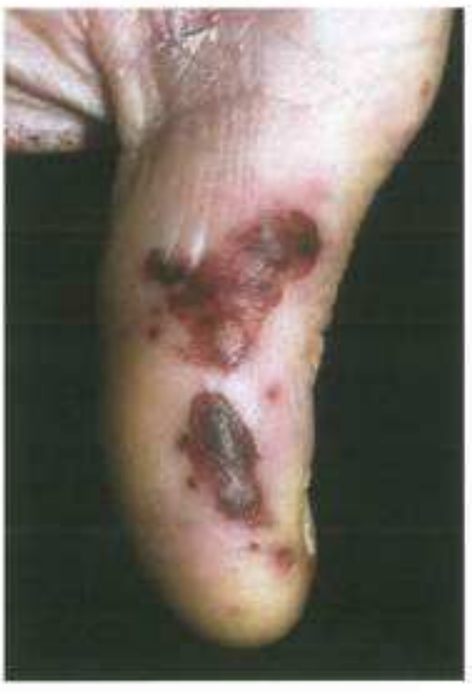


Fig. 18.38 Infective endocarditis. This patient has purpuric infarcts of the digits secondary to septic thromboembolism from infective endocarditis.

due to immune complex deposition and there is a pronounced skin involvement either alone (*leucocytoclastic vasculitis*) or as part of a specific syndrome known as *Henoch–Schönlein purpura* which involves the joints, skin, gut and glomeruli.

The causes of vasculitis may be categorized as follows:

- **Infection**
  - Bacterial e.g. *Neisseria* and staphylococcal/streptococcal endocarditis
  - Rickettsia
  - Viral e.g. hepatitis B and C
  - Mycobacteria e.g. *M. lepnae*
- **Immunological**
  - Immune complex
    - Henoch–Schönlein
    - Cryoglobulinaemia
    - Connective tissue disorders
    - Serum sickness
    - Paraneoplastic e.g. myelodysplastic syndrome
    - Drugs
    - Behçet's
  - Direct antibody
    - Goodpasture's syndrome
    - Kawasaki
  - ANCA
    - Wegener
    - Microscopic polyarteritis
    - Churg–Strauss syndrome
  - T cell mediated
    - Graft-versus-host rejection
- **Unknown**

It is critical thus to rule out first an infection such as meningococcaemia, hepatitis or Rocky Mountain spotted fever. There are several mechanisms involved in infection-associated purpuric lesions. These include direct invasion or damage to the vessel wall by the infecting organism or its toxins, septic emboli, immune complexes and disseminated intravascular coagulation. The differentiation of infectious causes is clearly important from immunological ones because their management is different.

The immune complex-mediated disorders may be due to cryoglobulins, serum sickness and IgA in Henoch–Schönlein purpura. Antineutrophil cytoplasmic autoantibodies (ANCA) are found in microscopic polyarteritis, Wegener's granulomatosis and the Churg–Strauss syndrome. Drugs, particularly sulphonamides, non-steroidal anti-inflammatories and anticonvulsants may cause an immune complex type of vasculitis known as a hypersensitivity cutaneous leucocytoclastic angiitis. Connective tissue disorders such as lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome may produce leucocytoclastic vasculitis. Behçet's syndrome may also and it is occasionally seen as a paraneoplastic phenomenon, particularly with haematological malignancies.

The type of infiltrate involved in the vasculitis may be helpful in ascertaining the diagnosis.

- **Leucocytoclastic** This is the commonest cutaneous form. The skin may be involved alone or with other systems, particularly the joints, gastrointestinal tract and kidneys. If there is an intense neutrophil infiltration, a condition known as *Sweet's syndrome* (*acute febrile neutrophilic dermatosis*; see below) results. Other neutrophilic dermatoses include pyoderma gangrenosum and the skin lesions associated with Behçet's syndrome and bowel-associated arthritis. If there is extensive complement activation associated with the immune complexes of a leucocytoclastic vasculitis, focal oedema and urticaria may result, producing a clinical picture of an urticarial vasculitis. A number of these patients have hypocomplementaemia and some also have lupus erythematosus.
- **Granulomatous** This is seen in Wegener's granulomatosis and also in chronic infections such as leprosy, syphilis or tuberculosis.
- **Bacterial** In meningococcaemia, the Gram-positive meningococci are found in the endothelial cells and neutrophilic infiltrate. In Rocky Mountain spotted fever, *Rickettsia* invade the endothelial cells, causing vascular destruction and initiating a mononuclear leucocyte infiltration.
- **Lymphocytic** This may be seen in some drug eruptions and pityriasis lichenoides chronica.
- **Eosinophilic** Eosinophils may dominate the vasculitis as in granuloma faciale, Well's syndrome (qv) and hypereosinophilic syndrome (qv).

Skin symptoms

The physical signs of vasculitis centre around the purpura, which is palpable. Depending on the degree of liquefaction necrosis in the dermis that occurs as a result of the vasculitis, there may be vesicles, pustules or, rarely, bullae. Nodules such as seen in polyarteritis nodosa occur as an extension of the mural vascular inflammation into the surrounding tissues. The nodules are usually hot, tender and red and may be surrounded by livedo reticularis. Nodules are seen when a vessel greater than the size of an arteriole is involved so are particularly seen in polyarteritis nodosa. Nodules occur in Churg–Strauss syndrome and in Wegener's granulomatosis but this is often granulomatous inflammation occurring extravascularly. They occur too in rheumatoid vasculitis and may resemble pyoderma gangrenosum, erythema nodosum or Sweet's disease.

Diagnosis

Patients with a presumptive diagnosis of vasculitis need to be investigated. Biopsy material should be examined pathologically, microbiologically and for immunoreactors. Serological tests are an important part of the immunological work-up and include tests for the antinuclear factor, rheumatoid factor, cryoglobulins, antineutrophil cytoplasmic autoantibodies (ANCA), complement levels, anti-C1q antibodies and immunoglobulins.

In the differential diagnosis of vasculitis are a number of disorders that may conveniently be called *vasculopathies*. They are often associated with the distinctive physical sign of a net-like (or reticulate) pattern known as livedo reticularis. This may occur as a physiological phenomenon but the relevance of it to this discussion is that it may occur as a necrotizing phenomenon as part of hyperviscosity states, for example in the antiphospholipid antibody syndrome, polycythaemia rubra vera, the macroglobulinaemias and embolic phenomena secondary to cholesterol or atheroma. Livedo reticularis may also be seen in association with large/medium vessel vasculitis such as polyarteritis nodosa and it is seen particularly in a distinctive syndrome known as *livedoid vasculopathy*, which has also been known as cutaneous polyarteritis nodosa or in hyperviscosity states and in vasculitis.

Purpura fulminans was a term used to describe a rapidly progressive skin necrosis following a normally benign infection such as chickenpox but is now known to be part of *disseminated intravascular coagulation* and involves organs other than the skin and is associated with hypotension and septic shock (see below). It is seen with certain infections, with protein C and S deficiency and in the lupus anticoagulant syndrome.

Other vasculitides described in this chapter include pityriasis lichenoides (which is characterized by an infiltration of dermal capillaries with small lymphocytes associated with endothelial proliferation), pigmented purpuric eruptions (characterized by endothelial swelling of the capillaries and a perivascular predominantly lymphocytic infiltrate associated with red cell extravasation), papular acrodermatitis of childhood (a reactive condition of perivascular lymphocytes and histiocytes), graft-versus-host disease (specific T cell-mediated injury) and certain rare forms of vasculitis that include erythema elevatum diutinum, granuloma faciale and Degos' syndrome.

HENOCH–SCHÖNLEIN PURPURA

A generally short-lived, IgA-mediated, benign leucocytoclastic vasculitis of the skin and joints (Henoch), the gastrointestinal tract and kidneys (Schönlein), usually occurring in young people following an infectious prodrome.

Aetiology

The disorder is quite common, particularly in the spring. It frequently follows an upper respiratory infection. Beta-haemolytic streptococci have been isolated in some cases but not in all. No specific virus has been incriminated. There may be an IgA cryoglobulinaemia, raised amounts of IgA or deposits of IgA found in the blood vessels in the skin. It is the commonest vasculitis of childhood (Fig. 18.39), particularly affecting boys, but it also occurs in adults. It is also known as Henoch–Schönlein purpura, *allergic vasculitis* or anaphylactoid purpura. The skin may be the only manifestation of the disorder. The condition is usually self-limiting within a month but it may persist longer and a minority suffer recurrences. Prognosis is related to the degree of renal damage if present. A small percentage develop chronic renal insufficiency.

Clinical Features

Symptoms

There may be a mild, constitutional upset with a low-grade fever and headache. There is often an upper respiratory tract infection, which is followed by the acute polymorphic purpuric eruption.

Morphology

These are crops of purple papules, vesicles (Fig. 18.40), urticarial wheals and bullae, which lead to necrosis and sometimes ulceration.

Distribution

The buttocks (Fig. 18.41), ankles and legs (Fig. 18.42) are affected, and occasionally the arms and abdomen.

Systemic features

There are a number of non-cutaneous manifestations of the syndrome.

- **Joints** These are most frequently affected after the skin. Arthralgias, which may affect a single or several joints, present as flitting pains of the ankles, knees, elbows and occasionally hands and feet.

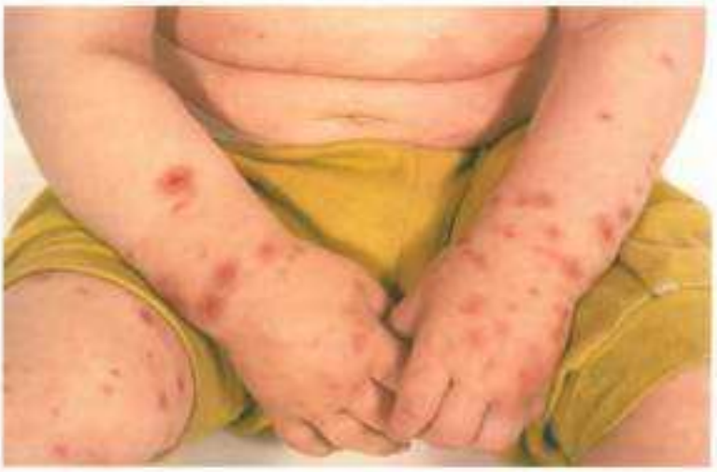


Fig. 18.39 Henoch–Schönlein purpura. The condition may affect young children, especially boys, and may involve the kidneys, gut and joints.

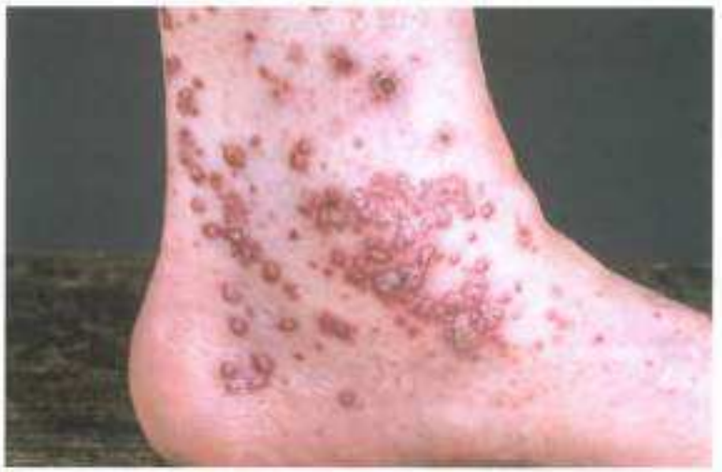


Fig. 18.40 Allergic vasculitis. Palpable purpuric lesions may be associated with renal, joint or gastrointestinal vasculitis, when the symptom complex is known as Henoch–Schönlein purpura. (Courtesy of St Mary's Hospital.)

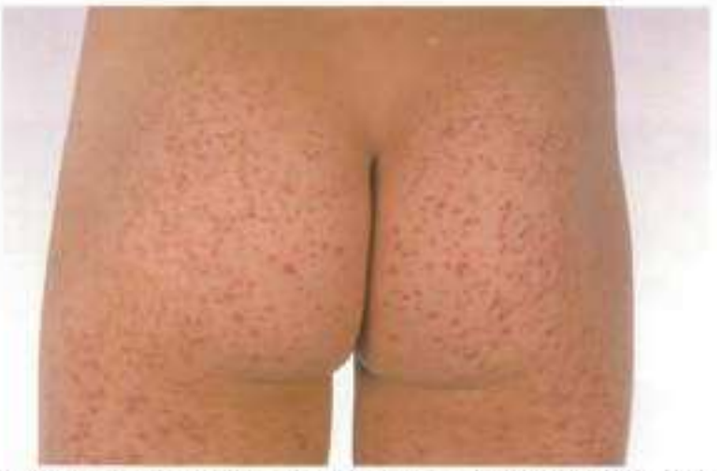


Fig. 18.41 Allergic vasculitis. Purpuric lesions on the buttocks are characteristic of Henoch–Schönlein purpura.

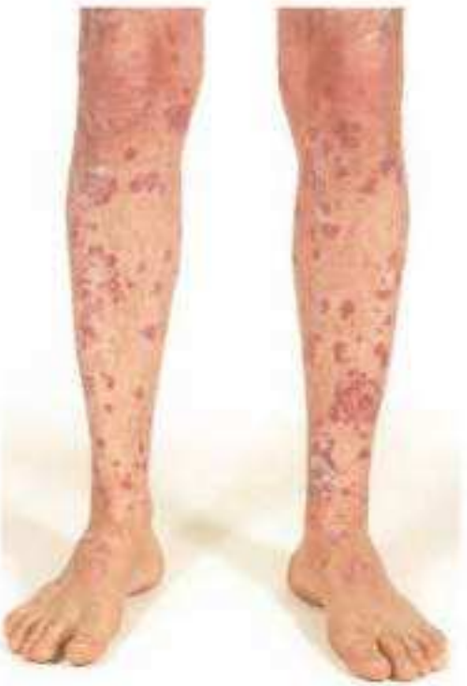


Fig. 18.42 Allergic vasculitis. The eruption occurs on the dependent parts, especially the lower legs and feet.

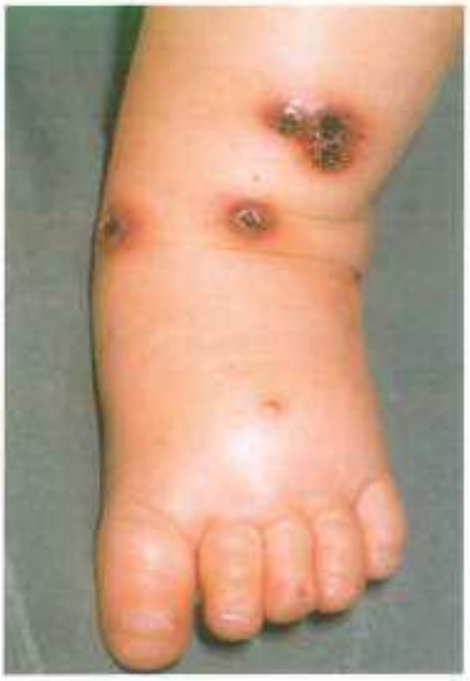


Fig. 18.43 Acute haemorrhagic oedema. This is a variant of Henoch–Schönlein purpura occurring in children under the age of 2. There are areas of circinate rosette like necrotic purpura on acral areas including the face.

- **Nervous system** Neurological abnormalities occasionally occur.
- **Lungs** Impairment of pulmonary diffusion is sometimes seen.
- **Gastrointestinal tract** There may be dull, abdominal (particularly peri-umbilical) pain and bloody diarrhoea in about half the patients. It may be the initial presenting symptom.
- **Kidneys** Renal involvement occurs later but not usually after 3 months. There is microscopic haematuria and proteinuria, which may proceed to nephrotic syndrome, nephritis and occasionally renal failure.
- **Infantile form** There is an infantile variant known as *acute haemorrhagic oedema*, which is manifested by a circinate purpura (Fig. 18.43) that is rather rosette-like with a dark almost necrotic centre. There is a tender oedema of the face, scrotum and acral extremities, although the skin symptoms are alarming and extensive, the child is not ill and no other system is usually involved. The histology is of a small vessel vasculitis and IgA deposits are found in a third but other immunoglobulins are also detected. It responds to systemic steroids.

Management

A throat swab may be positive for infection with a group A β-haemolytic streptococcus. The ESR, polymorphonuclear cell count and antistreptolysin O (ASO) titre is usually raised. Skin biopsy is necessary to confirm the presence of a leucocytoclastic vasculitis. The small blood vessels of both the papillary and reticular dermis are dilated, occluded and show fibrinoid necrosis (Fig. 18.44) with free red blood cells (Fig. 18.45). The vessel walls are infiltrated with a large number of neutrophil polymorphs and nuclear dust is present. Granular deposits of IgA, C3 and fibrinogen are found within the walls of the dermal vessels in the majority of patients. IgM and IgG may also be present (gastrointestinal biopsy may also show IgA in the blood vessel walls). The urine should be examined for haematuria and proteinuria. If these are positive, full renal assessment is indicated.

Henoch–Schönlein purpura is self-limiting within a month although a third of patients relapse and there may be recurrences after a year in about 10%. The prognosis is determined by the presence or absence of nephropathy. For the routine patient, rest, analgesia (non-steroidal anti-inflammatories) and penicillin as treatment of the streptococcal infection is all that is usually required. Systemic steroids are usually reserved for those with renal involvement.

In adult patients with leucocytoclastic vasculitis and no evidence of any other system involvement (i.e. patients with the cutaneous manifestations only of Henoch–Schönlein purpura), systemic steroids, colchicine and dapsone are often used to control the symptoms until the condition goes into remission.

Leucocytoclastic vasculitis can occur in a number of conditions including *cryoglobulinaemia* (Figs 18.46 and 18.47). Cryoglobulins are immunoglobulins with a tendency to precipitate at temperatures below 37 °C. Cryoglobulinaemia can be primary (mixed essential) or secondary to disorders such as lymphoproliferative disease, connective tissue disease or infections. There are three types of cryoglobulinaemia, with 50% of cases involving type III. In the mixed types, there are smaller amounts of cryoprecipitates that deposit and lead to vasculitis of the skin, joints, glomeruli and nervous system. Causes include autoimmune and lymphoproliferative disorders, infections (glandular fever, syphilis, borreliosis, hepatitis B and C, leprosy, kala-azar and subacute bacterial endocarditis). The cutaneous signs are of a palpable purpura with or without ulceration, urticaria and sometimes livedo reticularis. Morbidity is related to occlusion of the vasculature, leading to ischaemia or infarction. In all types it is triggered or aggravated by exposure to cold.

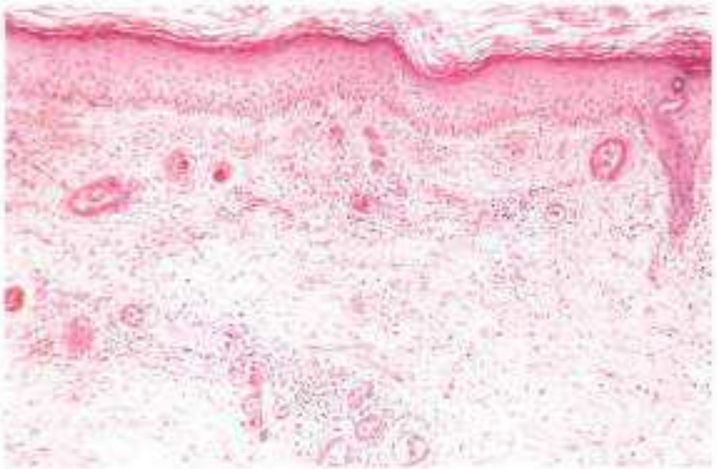


Fig. 18.44 Leucocytoclastic vasculitis. The small blood vessels of both the papillary and reticular dermis are dilated and show florid fibrinoid necrosis. There is marked extravasation of red blood cells into the connective tissue.

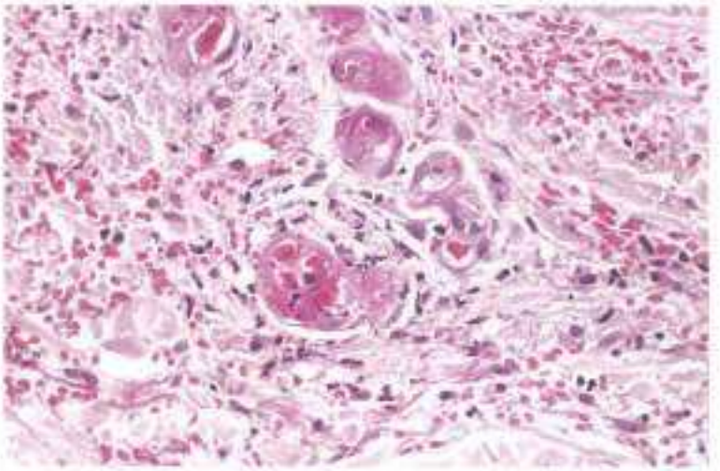


Fig. 18.45 Leucocytoclastic vasculitis. There is infiltration of the venule wall and perivascular connective tissue by large numbers of neutrophil polymorphs and darkly staining nuclear dust (leucocytoclasis). The vessels are partially occluded and there is extravasation of red blood cells.

Fig. 18.46 Cryoglobulinaemia. There is palpable purpura often in a reticulate pattern, triggered or aggravated by exposure to cold. This was precipitated by a hepatitis B infection.

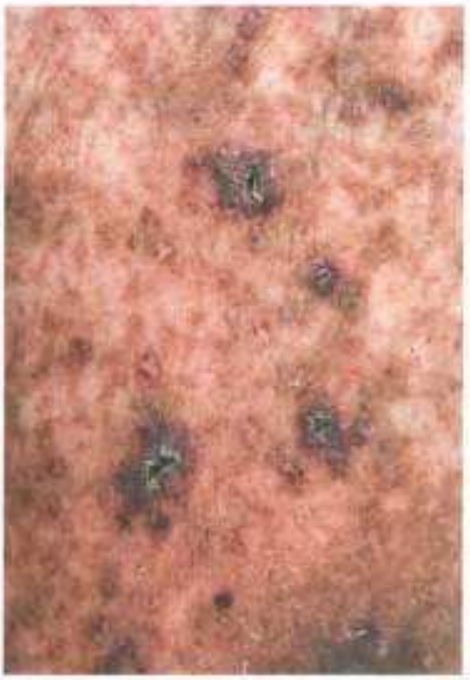


Fig. 18.47 Cryoglobulinaemia. This close-up of Fig. 18.46 shows the purpuric papules and the haemosiderin discoloration as the lesions heal.

SERUM SICKNESS

A syndrome of fever, urticaria, lymphadenopathy, myalgia and arthralgia following the administration of heterologous serum.

Aetiology

The urticaria of serum sickness is probably a manifestation of an immune complex-mediated necrotizing vasculitis coupled with the activation of complement. Although classically it follows the administration of heterologous serum (for example horse or rabbit to treat aplastic anaemia), a similar reaction occurs to blood, plasma or immunoglobulin fractions. Many of these latter patients have IgG antibodies to IgA. Drugs may induce a similar clinical picture, including sulphonamides, penicillins, non-steroidal anti-inflammatory drugs, anticonvulsants, thiouracils and streptokinase.

Clinical Features

Symptoms

The condition occurs 7 to 12 days after the heterologous serum and lasts for about a week. If the patient has been previously exposed, the reaction occurs within a couple of days.

Morphology

Most patients with serum sickness have urticaria (Fig. 18.48), which often begins at the site of an injection and lasts longer than true urticaria. Palpable purpura and angio-oedema may be present.

Distribution

The urticaria becomes widespread.

Systemic features

Lymphadenopathy, arthralgias, arthritis, fever and hypocomplementaemia are other features of the syndrome.

Management

The cause should be established and the patient advised never to have the offending agent again. Systemic steroids may be of benefit.

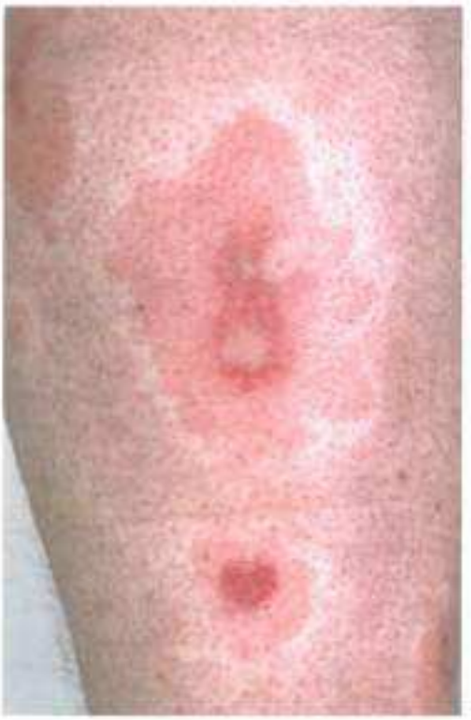


Fig. 18.48 Urticarial vasculitis. Urticarial lesions persist for several days, unlike ordinary urticaria. Biopsy revealed a vasculitis.

PURPURA FULMINANS

A rapid progressive haemorrhagic necrosis of the skin with haematological features of a severe disturbance of the coagulation mechanism (*disseminated intravascular coagulation*) that results in various combinations of bleeding, thromboembolism and haemolytic anaemia.

Aetiology

The condition is caused by failure of the normal inhibitory mechanisms of clotting, which leads to intravenous coagulation, followed by consumption and depletion of platelets and plasma clotting factors. The usual

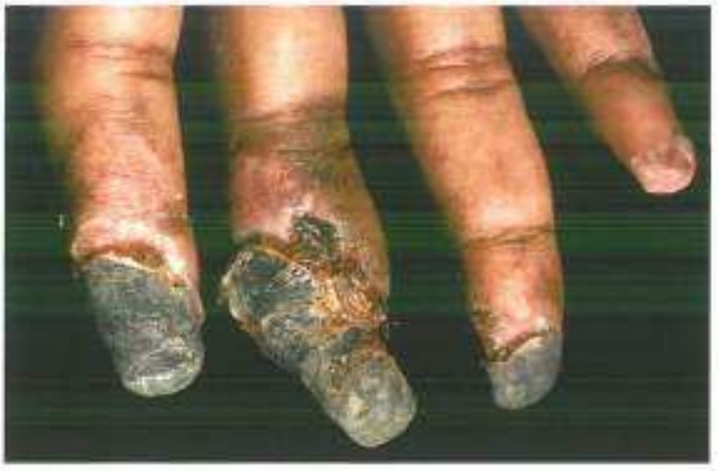


Fig. 18.49 Purpura fulminans. Extensive acral necrosis and gangrene may occur in disseminate intravascular coagulation associated with meningococcaemia.

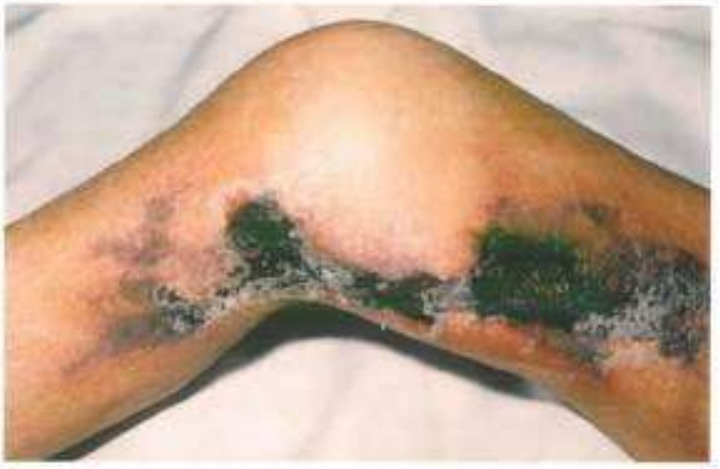


Fig. 18.50 Purpura fulminans. Lakes of purpura and necrosis are present. This patient had protein C and S deficiency.

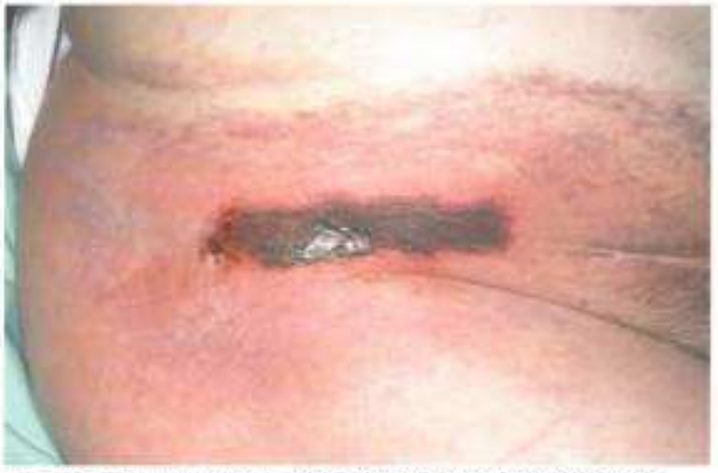


Fig. 18.51 Purpura fulminans. The buttocks and thighs are affected in this patient in association with warfarin necrosis.

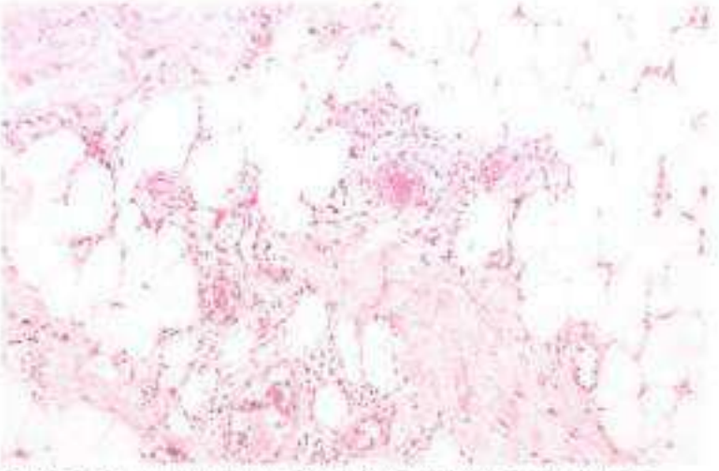


Fig. 18.52 Purpura fulminans. Fibrin thrombi are present in small venules.

causes are obstetric complications, extensive tissue damage, severe infections (in particular Gram-negative septicaemia), immune reactions or malignant disease.

Purpura fulminans was initially used to describe rapidly progressive skin necrosis following a benign infection such as chickenpox or a streptococcus. Significant thrombosis or haemorrhage in organs other than the skin was unusual. The concept has now been extended to cutaneous necrosis associated with haematological features of disseminated intravascular coagulation and may be associated with protein C and S deficiencies, the antiphospholipid syndrome and sepsis. The organisms most frequently involved are *Neisseria meningitidis* (Fig. 18.49), Gram-negative bacilli, Gram-positive cocci and *Rickettsia* sp. Necrosis is more acral than in the classical form and progresses in an ascending fashion. It is associated with haemorrhagic necrosis of internal organs and there is hypotension and septic shock.

Protein C is a vitamin K plasma glycoprotein made in the liver. It is activated by thrombin and then has an anticoagulant activity. Deficiency leads to a hypercoagulable state. This may be acquired in association with sepsis or be inherited as an autosomal dominant. In the homozygous state there is a neonatal purpura fulminans and disseminated intravascular coagulation. In the heterozygous state, there is often a history of recurrent deep vein thrombosis in young adults and the skin necrosis occurs in association with oral anticoagulants such as coumarins. Consumption of protein S may also occur in purpura fulminans (Fig. 18.50).

Clinical Features

Symptoms

The patient is ill with a high fever and general systemic upset.

Morphology

Extensive symmetrical lakes of purpura develop acutely.

Distribution

The extremities are involved in sepsis-associated disease and the buttocks and thighs are more usually involved in the classic form secondary to an antecedent benign infection and in congenital protein C and S deficiencies and warfarin necrosis (Fig. 18.51).

Management

The clinical diagnosis is not difficult. Skin biopsy shows occlusion of dermal capillaries and venules with thrombi and haemorrhage and varying degrees of cutaneous infarction and necrosis (Fig. 18.52). Coagulation studies (international normalized ratio (INR), activated partial thromboplastin time (APTT) and fibrin degradation products (FDP)) are abnormal. The management is treatment of the cause and of the shock, and replacement of coagulation factors with fresh frozen plasma or prothrombin concentrates in conjunction with heparin. Protein C concentrates are also used in association with acquired protein C deficiency. In extreme cases, the disorder is fatal within a few days but less severe changes do occur.

ACUTE FEBRILE NEUTROPHILIC DERMATOSIS

Acute febrile neutrophilic dermatosis (Sweet's syndrome) is an acute systemic illness with fever, polymorphonuclear leucocytosis and inflammatory skin lesions with a characteristic neutrophilic histology.

Aetiology

There are five types:

- Idiopathic, usually middle-aged females, occasionally following an upper respiratory tract infection.
- Paraneoplastic, most often associated with the myelodysplastic syndrome (MDS), myeloproliferative disorders and acute myeloid leukaemia.
- Parainflammatory, in association with Crohn's disease, ulcerative colitis, Behçet's, SLE and Sjögren's.
- Infection, particularly *Yersinia*, *Salmonella*, toxoplasmosis, histoplasmosis, mycobacteria and coccidioidomycosis.
- Granulocyte-stimulating growth factor (GCSF) may precipitate the process and elevated serum levels have been demonstrated in the acute phases of Sweet's syndrome. Over-expression of GCSF may be compensatory and secondary to impaired haematopoiesis in MDS.
- It can occur in pregnancy.

Clinical Features

Symptoms

There is a high, persistent fever (suggestive of septicaemia), arthralgia, conjunctivitis, episcleritis and aphthosis associated with tender skin lesions.

Morphology

There are well-defined, erythematous or plum-coloured, indurated, tender plaques (Fig. 18.53) or nodules (Figs 18.54 and 18.55). Pustules and haemorrhagic blisters may form, particularly in the non-idiopathic types.

Distribution

Trunk, upper extremities, face and neck, and a variant limited to the dorsa of the hands (*neutrophilic dermatosis or pustular vasculitis of the hands*; Fig. 18.56).

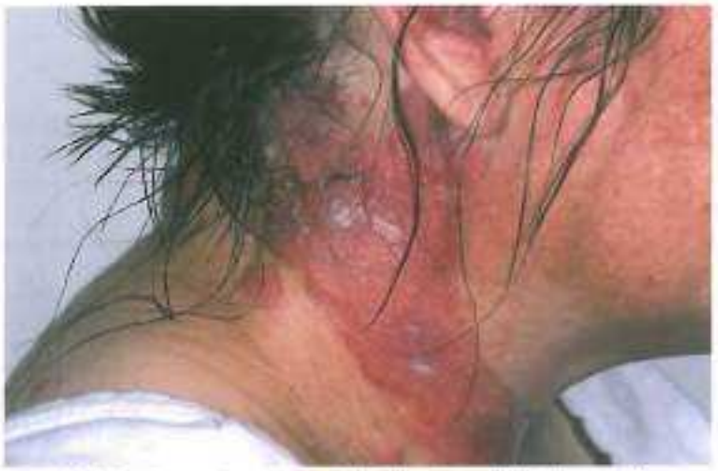


Fig. 18.53 Sweet's syndrome. This lady had acute myeloid leukaemia. The lesions were associated with a high fever and treated with intravenous antibiotics until the correct diagnosis was made and confirmed by biopsy.

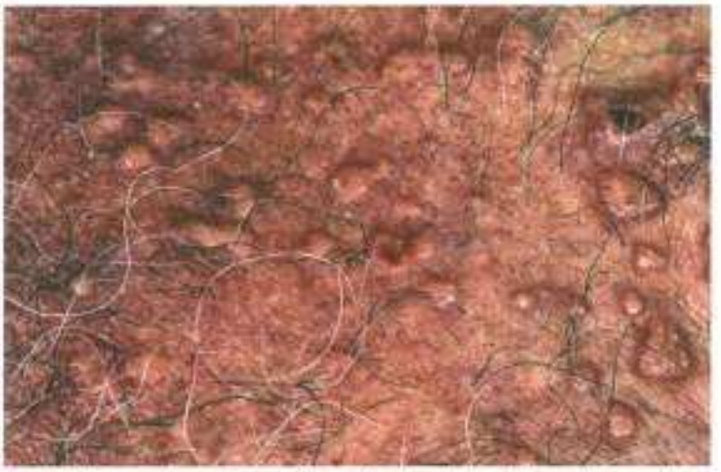


Fig. 18.54 Sweet's syndrome. This man had myelodysplastic syndrome and had recurrent and persistent lesions. It was refractory to treatment other than systemic steroids.

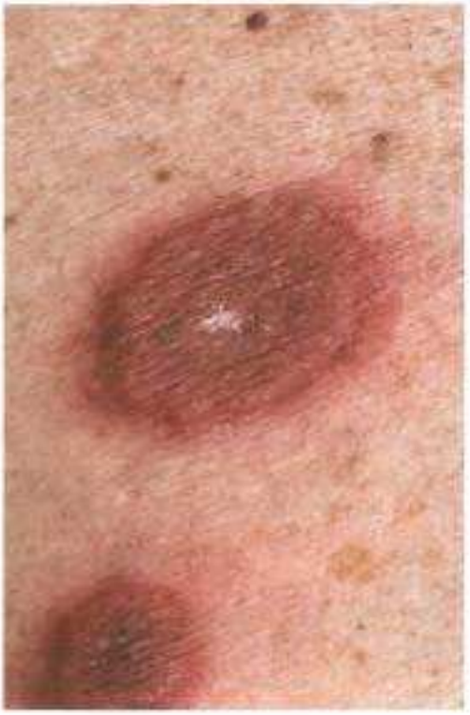


Fig. 18.55 Sweet's syndrome. The lesions are well-defined, indurated tender plaques often associated with a high fever. This lady had recurrent attacks over many years, but no cause has yet been found.

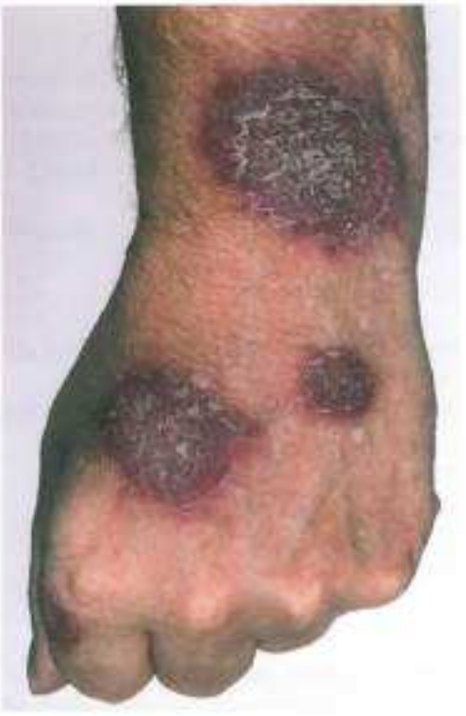


Fig. 18.56 Sweet's syndrome. The condition may be confined to the backs of the hands and is known as neutrophilic dermatosis of the hands. He had myelodysplastic syndrome.

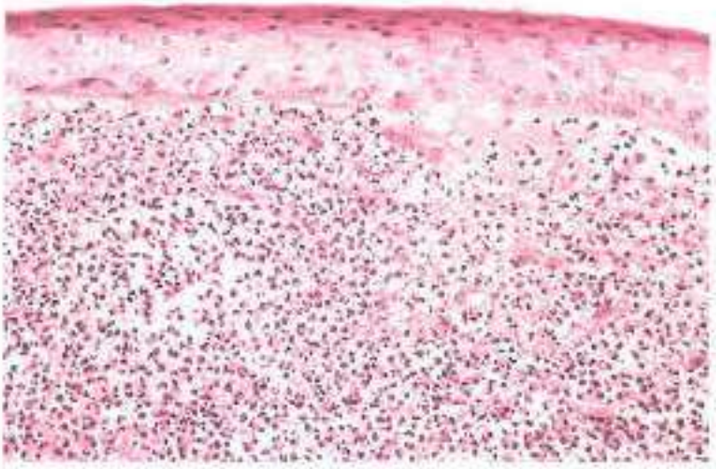


Fig. 18.57 Sweet's syndrome. The superficial dermis contains an intense, usually band-like neutrophilic infiltrate, and occasionally secondary leucocytoclastic vasculitis.

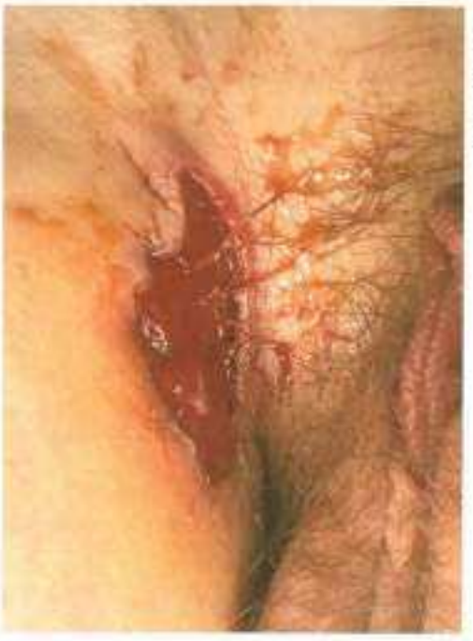


Fig. 18.58 Pyoderma gangrenosum. The ulcer has an undurated purple margin. This woman had associated rheumatoid arthritis.

Management

There is a polymorphonuclear leucocytosis, and a raised ESR. There is sometimes proteinuria and a positive ANCA. The histology of the skin lesions is characteristic and shows an early, dense, dermal infiltrate of neutrophils (Fig. 18.57), followed later by lymphocytes. Sometimes the infiltrate is composed of histiocytoid mononuclear cells (which are shown to be immature myeloid cells with myeloperoxidase immunohistochemistry). There may or may not be vasculitis. There are no organisms to be found. The patient should be investigated for an underlying cause. The lesions respond to systemic steroids. Ciclosporin, rapamycin, dapsone, minocycline, interferon and indomethacin have all been described as being helpful. Idiopathic cases do have a tendency to recur.

PYODERMA GANGRENOSUM

A destructive non-infective inflammatory skin disorder that results in ulceration of the skin, high fever and toxicity; it is often associated with disordered immune function.

Aetiology

The exact mechanism is unknown. Both humoral and cell-mediated immunity may be at fault. It may be an autoimmune disorder because of its association with other autoimmune processes. There is pathergy and it can be provoked by minor trauma (as happens in Behçet's disease). A quarter are idiopathic. Many patients have an underlying cause:

- Crohn's disease, ulcerative colitis, rheumatoid arthritis, Behçet's syndrome
- Hepatitis
- Diabetes
- Wegener's
- Monoclonal gammopathies, hypogammaglobulinaemia, plasma cell dyscrasias, multiple myeloma
- Acute leukaemia, myelodysplastic syndrome, polycythaemia rubra vera
- T cell abnormalities.

Clinical Features

Symptoms

The patient is toxic with a high fever.

Morphology

There are two presentations:

- There may be a painful, tender, red nodule that becomes blue centrally, often with a superficial pustule or blister. The lesions become turgid and ulcerate fairly rapidly (Fig. 18.58). The edge of the ulcer is often bluish in colour and raised, with an undermined overhanging edge (Figs 18.59 and 18.60). There may be a surrounding erythema in the early stages. The ulceration heals by scarring.
- Alternatively the eruption may be more superficial, presenting as a vegetative pyoderma, associated with pustules (Fig. 18.61).

Distribution

Usually on a leg but occasionally elsewhere, arising de novo or following minimal trauma. It is often mistaken for sepsis, including necrotizing fasciitis, and debrided. The superficial form may occur anywhere and sometimes at the site of a pre-existing skin disorder.

Management

Pyoderma gangrenosum is distinguished from sepsis by negative cultures of skin and blood for bacteria, mycobacteria and fungi. The histology is not pathognomonic, but there may be large sterile abscess formation with venous and capillary thrombosis, haemorrhage, necrosis and a massive cellular infiltrate, particularly of polymorphoneutrophils. Usually no evidence of primary vasculitis is seen. The management is that of the cause of the condition. Many of the haemorrhagic bullous forms are associated with acute leukaemia or polycythaemia rubra vera and have overlapping clinical features with Sweet's syndrome. The skin lesions do respond rapidly to high-dose systemic glucocorticosteroids. Some patients respond to minocycline, ciclosporin, mycophenolate mofetil or infliximab. A variant is associated with acne and arthritis and known as the PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne).

ERYTHEMA ELEVATUM DIUTINUM

A rare, localized chronic leucocytoclastic vasculitis on the backs of the hands and over the extensor surfaces of certain other joints.

Aetiology

Although often idiopathic, there is an association with myeloma, monoclonal gammopathies (especially IgA), myelodysplastic syndrome and HIV. It affects middle-aged men and women equally, although it occasionally occurs in young girls.

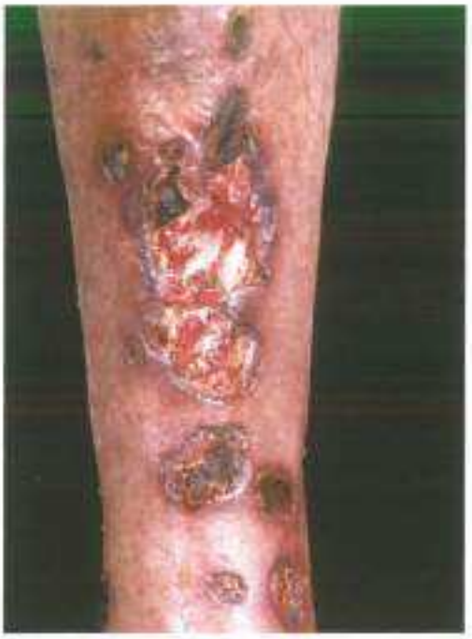


Fig. 18.59 Pyoderma gangrenosum. This ulcer has a blue, overhanging margin. The patient had ulcerative colitis. (Courtesy of St Bartholomew's Hospital.)

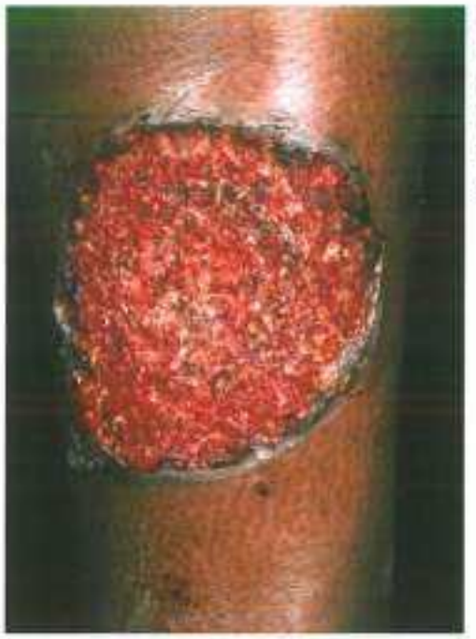


Fig. 18.60 Pyoderma gangrenosum. The onset was rapid. The lesion was painful. The oedematous purple margin of the ulcer is typical of pyoderma gangrenosum.

The histology is fairly characteristic. It consists of a dense, predominantly neutrophilic, perivascular infiltrate with some eosinophils, mononuclear cells and plasma cells. Leucocytoclasis may be present, the endothelial cells are swollen and the vessel walls are surrounded by a coat of eosinophils. Subsequently granulation tissue, fibrosis and deposition of lipid material are found.

Clinical Features

Symptoms

Unsightly skin nodules and occasionally arthralgia.

Morphology

Red or purple plaques (Fig. 18.62) that are infiltrated and soft at first but become hard as the lesions fibrose. They ultimately disappear without scarring but leave postinflammatory pigmentation.

Distribution

Roughly symmetrical, particularly over the backs of the knuckles but also on the elbows and knees (Fig. 18.63), wrists, ankles and buttocks.

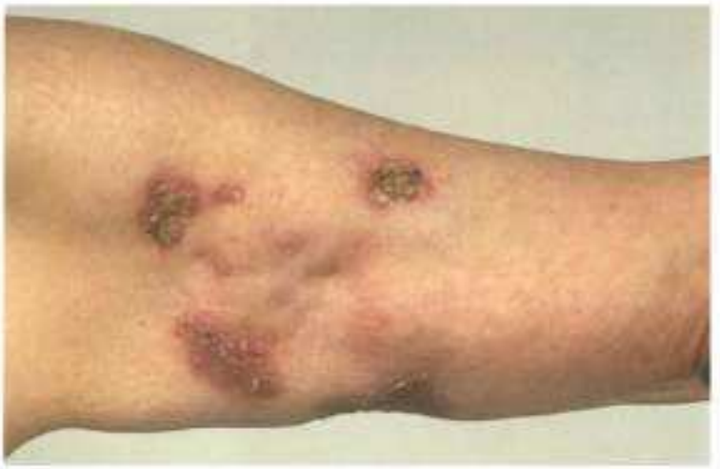


Fig. 18.61 Superficial granulomatous pyoderma. There are nodular abscesses that discharge pus. This responded to minocycline.

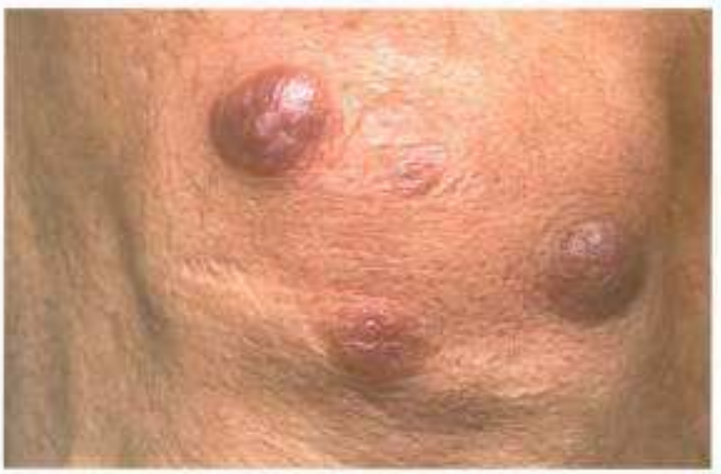


Fig. 18.62 Erythema elevatum diutinum. Chronic purple plaques or nodules occur particularly over the knees.

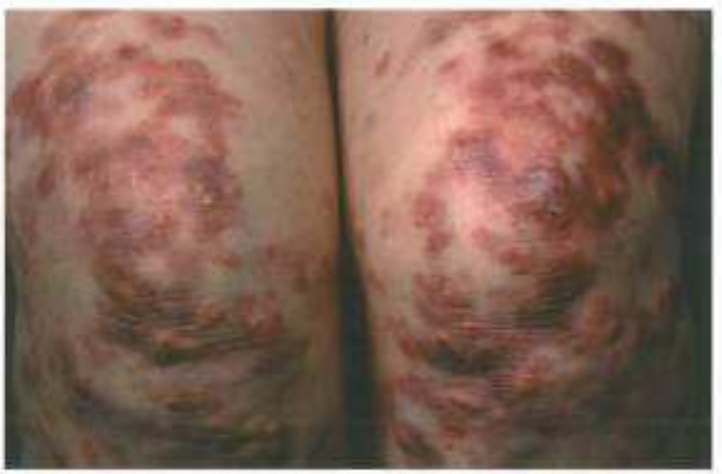


Fig. 18.63 Erythema elevatum diutinum. This lady had extensive florid and painful lesions which in part were typical of erythema elevatum diutinum (seen here), Sweet's and pyoderma gangrenosum. She had early myelodysplastic syndrome but succumbed from her lesions.

Management

The lesions are rather characteristic but a skin biopsy aids confirmation of the diagnosis. This chronic, low-grade vasculitis is difficult to treat if no cause is found but spontaneous clearing does occur sometimes. Dapsone is commonly used.

GRANULOMA FACIALE

A rare localized eosinophilic-rich vasculitis affecting the face.

Aetiology

The cause is unknown. It may be an immune complex disorder. IgG, IgA, IgM and C3 have been demonstrated with the blood vessel walls. There is an eosinophil-rich vasculitis.

Clinical Features

Symptoms

The lesions occasionally burn.

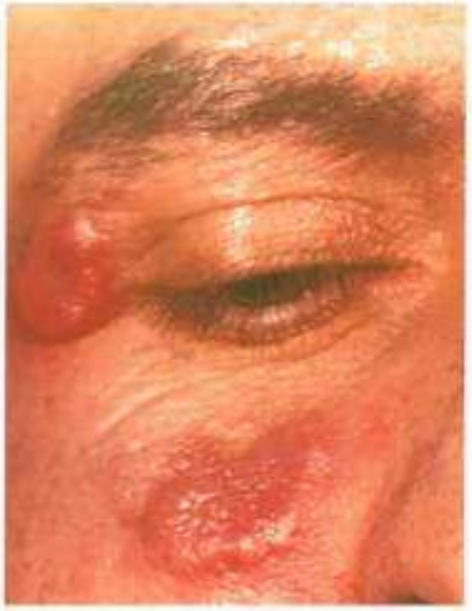


Fig. 18.64 Granuloma faciale. Asymptomatic, single or multiple, red-brown nodules occur on the face.

Morphology

Soft, well-defined plaques or nodules that may be red-brown, purple or flesh coloured. The follicular openings are prominent and there are sometimes telangiectasia and scaling.

Distribution

The nose, forehead or cheeks (Fig. 18.64). They may be single or multiple.

Management

Histologically, there is a dense polymorphous infiltrate of eosinophils and neutrophils (Fig. 18.65), often with leucocytoclasis, particularly in the upper dermis but sometimes more deeply. There are also histiocytes, lymphocytes, plasma cells and mast cells. Vasculitis may sometimes be evident. A characteristic feature is the separation of the epidermis and the skin appendages from the infiltrate by a narrow Grenz zone of normal collagen.

It may respond to intralesional steroids, cryotherapy or lasers. Topical psoralen plus ultraviolet A (PUVA), surgical excision, dapsone and clofazimine may also be tried.

Panniculitis

The subcutaneous fat (panniculus) serves as a thermal and mechanical insulator. It consists of fat cells (lipocytes) arranged into lobules that are surrounded by fibrous septa containing blood vessels, lymphatics and nerves. The blood vessels cross the lobules and surround each lipocyte with a capillary network.

Inflammatory disorders of the subcutaneous fat may involve either the lobules or septa, or both, and may do this in the absence or presence of vasculitis. Traditionally they are classified on this basis, but this may be somewhat artificial as more causes are elucidated. Clinically the picture is of tender red subcutaneous nodules, which may or may not break down or ulcerate (e.g. α1-antitrypsin deficiency) or produce an oily discharge (e.g. pancreatic panniculitis) (Fig. 18.66). The causes are:

- **Lobular**
  - Physical (cold, injections)
  - Neonatal (subcutaneous fat necrosis of the newborn, sclerema neonatorum)
  - Post systemic steroids
  - Connective tissue disorders (lupus profundus, dermatomyositis)
  - Pancreatic
  - Infection
  - T cell lymphoma panniculitis

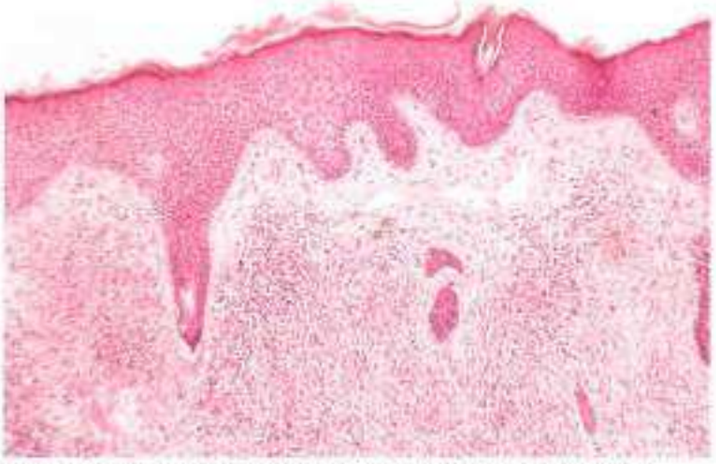


Fig. 18.65 Granuloma faciale. A heavy mixed inflammatory cell infiltrate is evident. Note the sparing of the Grenz zone and the periadnexal connective tissue.

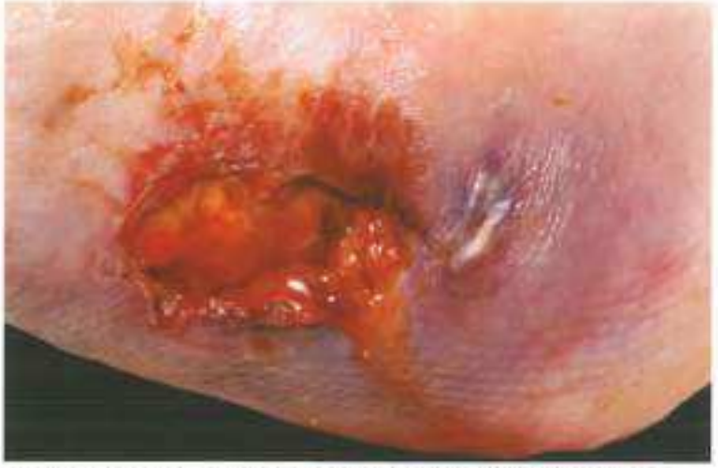


Fig. 18.66 Pancreatic panniculitis. Tender red subcutaneous nodules may break down and produce an oily discharge associated with pancreatitis or pancreatic cancer.

- **Septal**
  - Erythema nodosum
  - α_1-antitrypsin deficiency (may be mixed)
  - Panniculitis of morphoea/scleroderma
- **With vasculitis**
  - Erythema induratum
  - Nodular vasculitis

Of these, two should be noted:

- **α_1-antitrypsin deficiency**

  α_1-antitrypsin deficiency is a glycoprotein produced in the liver and is the most important circulating serine protease inhibitor (serpin), which acts upon a wide range of proteolytic enzymes, e.g. trypsin, elastase, collagenase, which degrade tissue. This inborn error of metabolism affects both sexes equally and presents at any time of life. There is severe painful panniculitis with an oily discharge and cirrhosis (due to retention of the molecule in the liver), emphysema, pancreatitis and rheumatoid arthritis. Intravenous replacement of α_1-antitrypsin is effective.

- **Pancreatic panniculitis**

  Subcutaneous nodules on the legs, arms, chest, abdomen and scalp occur with fever, arthritis and abdominal pain (involvement of visceral fat including the omentum and peritoneum) are associated with acute or chronic pancreatitis or pancreatic carcinoma. The lipase and amylase are raised and pathologically there is a mixed septal/lobular panniculitis with deposition of basophilic material due to saponification of fat by calcium salts.

Lobular panniculitis without vasculitis was originally known as Weber–Christian disease, subsequently as *relapsing febrile nodular panniculitis*. However, a number of specific causes of a similar picture of recurrent formation of single or multiple crops of tender nodules in the subcutaneous fat associated with various systemic features are now being identified. These include α_1-antitrypsin deficiency, pancreatic disease, autoimmune disease (connective tissue panniculitis leading to lipo-atrophy), histiocytic cytophagic panniculitis and subcutaneous T cell lymphoma.

Similar subcutaneous nodules may occur as a result of trauma, for example the injection of mineral oils, either by physicians or factitiously by patients. Individuals who wear non-insulated, often tight-fitting clothing in very cold weather may develop cyanotic, indurated, tender nodules, particularly on such sites as the buttocks and thighs.

In children, a panniculitis used to be described following the reduction of systemic steroids given particularly for rheumatic fever but this is now rarely seen.

Lobular panniculitis with vasculitis is classically seen in *erythema induratum* (*Bazin's disease*), which is associated with tuberculosis and manifests as tender red nodules on the backs of the calves which may ulcerate. More frequently, no cause is found and the condition is then known as nodular vasculitis.

Septal panniculitis without vasculitis occurs in erythema nodosum and also as part of a more general involvement, for example in eosinophilic fasciitis, where the inflammatory process affects the fascia and the reticular dermis as well as the septa of the subcutaneous fat.

A mixed panniculitis involving both the septa and lobules is particularly seen in lupus profundus and a clinical variant of sarcoidosis known as the Darier–Roussy sarcoid. Subcutaneous forms of granuloma annulare and lipodermatosclerosis show the same picture.

Lastly, panniculitis may occur as a consequence of vasculitis. This is seen in leucocytoclastic vasculitis and also in the vasculitides affecting larger vessels such as polyarteritis nodosa and in the superficial migratory thrombophlebitis associated with underlying malignancy. In nodular vasculitis and erythema induratum, there is also a panniculitis as a consequence of the vasculitis.

A rare, calcifying panniculitis may occur in association particularly with renal disease although occasionally with pancreatic disease, autoimmune disease or trauma. There are two types of calcifying panniculitis. The most common is seen in patients undergoing haemodialysis, where there is diffuse calcification of the media of small and intermediate size blood vessels. In the second type, there is considerable interstitial calcium deposition in the subcutaneous fat; this is particularly seen in calciphylaxis (systemic calcinosis – Ch. 22). The causes of panniculitis are determined by evaluation of the clinical context (an oily discharge suggests a pancreatic disorder), a deep surgical biopsy (essential for panniculitic lymphoma) and appropriate investigations for the conditions described above.

NODULAR VASCULITIS

A chronic recurrent condition of bilateral red, tender, subcutaneous nodules in the legs of middle-aged females.

Aetiology

This is a lobular panniculitis, which differs from erythema induratum of Bazin (associated with a focus of tuberculosis) because no cause is found. It occurs in middle-aged females, who often are obese, have venous insufficiency, are prone to thrombophlebitis and sensitive to cold weather.

Clinical Features

Symptoms

The lesions are painful but the patient is otherwise well.

Morphology

They are red, tender nodules, which may be up to 2 cm in diameter. There is a tendency for recurrent crops to appear.

Distribution

The lesions are bilateral and occur particularly on the calves (Fig. 18.67) but may also be seen on the shins, thighs and occasionally the arms.

Management

A skin biopsy may be helpful and it is useful to exclude all the known causes of erythema nodosum. However, the condition is different in that the latter disorder is an acute one whereas nodular vasculitis persists for an indefinite period of time. Treatment is unsatisfactory. Rest is of benefit and a multiplicity of treatments are used. Systemic steroids are effective but courses are necessarily prolonged. Agents such as potassium iodide, thalidomide, dapsone, adelat, aspirin and various immunosuppressants have been used.

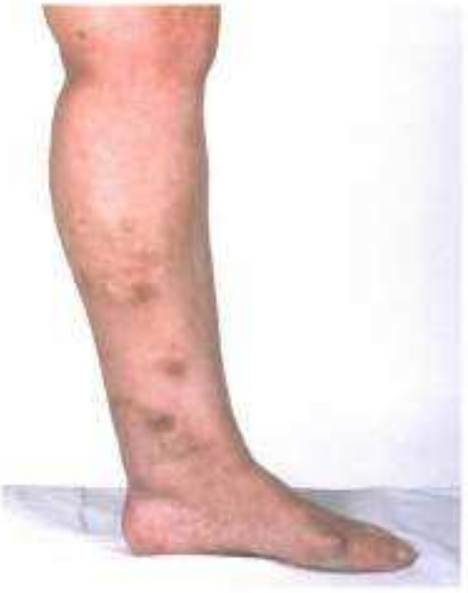


Fig. 18.67 Nodular vasculitis. This disorder simulates erythema nodosum but is chronic and occurs in middle-aged females with a perniotic circulation.

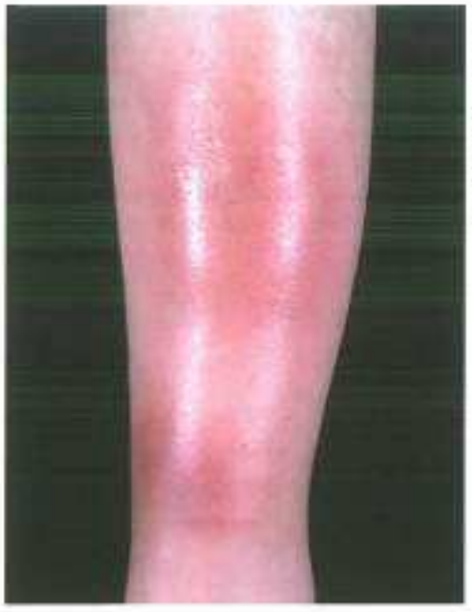


Fig. 18.68 Erythema nodosum. There are recurrent tender red nodules with an intact shiny smooth surface. Streptococcal infections and sarcoidosis are the commonest causes in the UK.

ERYTHEMA NODOSUM

An acute reactive disorder of crops of tender, red nodules on the lower limbs often associated with an identifiable trigger.

Aetiology

Erythema nodosum is relatively common and especially affects young, adult females. Potential causes vary with geographical location. Within the UK, sarcoidosis, streptococcal infections and drug eruptions are most to blame. The causes are:

- **Bacterial infections** especially *Streptococci*, tuberculosis, leprosy, syphilis, leptospirosis, *Yersinia* and *Salmonella* sp.
- **Viral and chlamydial infections** especially vaccinia, lymphogranuloma venereum, cat scratch disease, glandular fever, infectious mononucleosis and psittacosis
- **Fungal infections** especially blastomycosis, coccidioidomycosis, histoplasmosis and dermatophytes

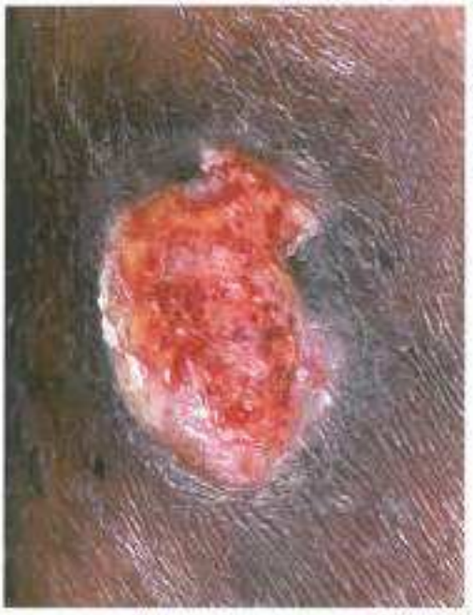


Fig. 18.69 Erythema induratum. In Bazin's disease associated with overt tuberculosis, tender nodules occur on the backs of the calves and ulcerate.

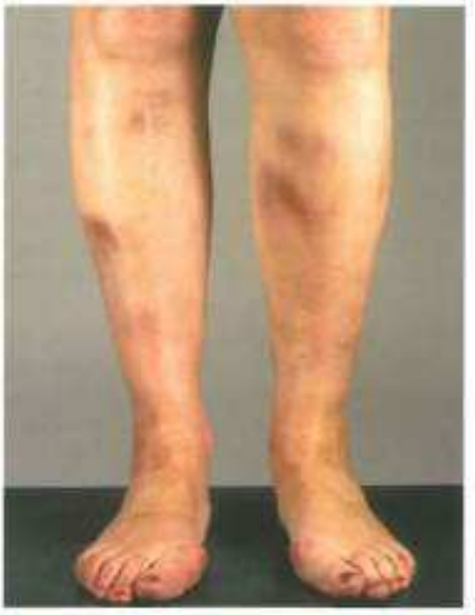


Fig. 18.70 Erythema nodosum. The lesions occur bilaterally on the legs, particularly the fronts of the shins.

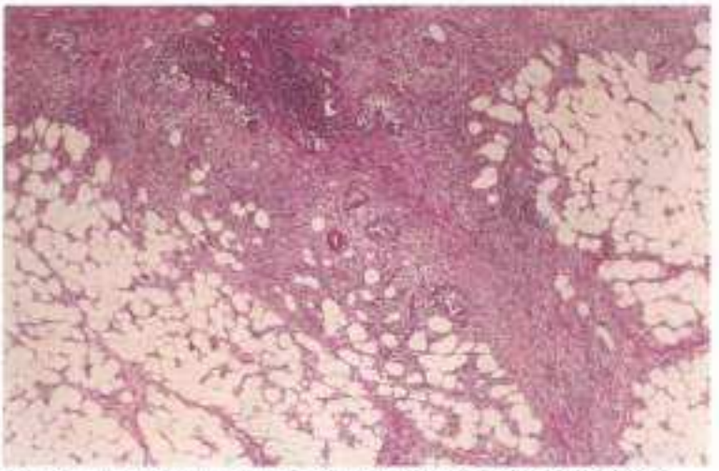


Fig. 18.71 Erythema nodosum. The essential features are those of a septal panniculitis: there is intense inflammation of the deep reticular dermis and fibrous septum with relative sparing of the fat lobules.

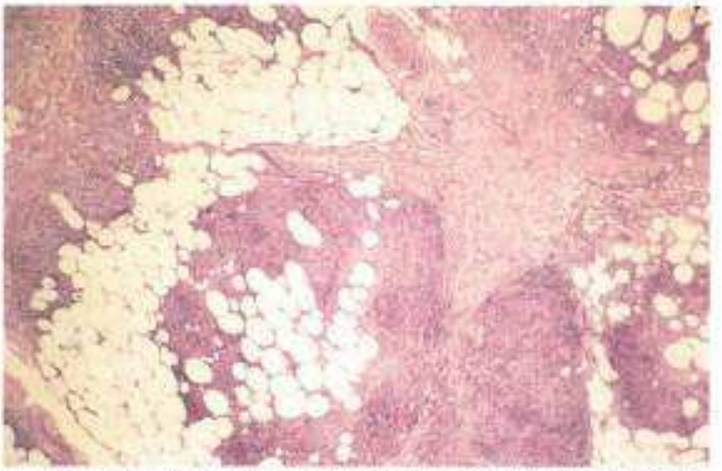


Fig. 18.72 Erythema induratum. A dense granulomatous infiltrate involves both the septae and adjacent lobules.

- **Drugs** especially barbiturates, sulphonamides, oral contraceptives and halogens
- **Systemic disorders** especially sarcoidosis, ulcerative colitis, Crohn's disease, Hodgkin's disease and Behçet's disease.

The condition appears to be an immunological reaction that can be precipitated by a wide range of antigens. In sarcoidosis, erythema nodosum is a well-known association with bilateral hilar adenopathy (Löfgren's syndrome). Tuberculosis is a very common cause in Third World countries. In these cases the nodules are often on the backs of the calves and may ulcerate. It is known as erythema induratum (Bazin's disease). *Mycobacterium tuberculosis* genes have been identified in the skin lesions by PCR. Sometimes, an identical clinical picture is seen in patients who have no overt signs of tuberculosis but have an unusually pronounced response to the Mantoux test at 1:10 000 and a past personal or family history of exposure to tuberculosis. Antituberculous therapy is often effective.

Clinical Features

Symptoms

An acute onset of painful red nodules, usually on the legs, associated with some malaise, joint pains and a slight fever.

Morphology

Crops of bright, tender, red shiny smooth-surfaced nodules (Fig. 18.68) appear, which subsequently go mauve. Individual lesions last 1–2 weeks and attain a diameter of 3–4 cm. They may ulcerate in erythema induratum (Fig. 18.69).

Distribution

The extensor surfaces of the shins (Fig. 18.70), but occasionally the calves, thighs and extensor aspects of the upper limbs. There is often ankle oedema.

Management

The clinical picture is readily recognized. Management involves identification and treatment of the cause. A full physical examination is necessary, and a full blood count, ESR, chest X-ray, ASO titre, Mantoux test, stool, urine and blood culture are all basic investigations. A skin biopsy may be helpful. In erythema nodosum, the essential histological features are of a septal panniculitis with relative sparing of the fat lobules (Fig. 18.71). The inflammation of the septa becomes granulomatous latterly. In erythema induratum, there are nodular granulomas in the fibrous septa and at the periphery of the lobules (Fig. 18.72). Vasculitis is present. The attack usually lasts 6 weeks in routine cases.

A rare variant of erythema nodosum is known as *erythema nodosum migrans* or subacute nodular migratory panniculitis (Vilanova's disease). The lesions are often unilateral and painless but resemble erythema nodosum in being erythematous nodules on the anterior lateral aspect of the lower leg. The nodule has a bright red edge with a yellow sclerodermoid centre and may attain quite a large size over a period of 2 or 3 weeks. Erythema nodosum migrans appears to affect particularly middle-aged females. The ESR and ASO titre are raised and the histology is septal panniculitis similar to that of erythema nodosum. It responds to potassium iodide within a few days.

POLYARTERITIS NODOSA

A serious systemic immune complex-mediated arteritis particularly involving the kidneys, cardiovascular system and nervous system and sometimes the skin.

Aetiology

There is a multisystem necrotizing vasculitis of small- and medium-sized vessels, which leads to thrombosis and infarction, embolism or rupture of the vessel wall. The condition is of unknown aetiology but the hepatitis B antigen (particularly patients on long-term haemodialysis with chronic hepatitis B antigenaemia), HIV and parvovirus have been implicated. The condition usually begins in middle age and it is more common in men.

Clinical Features

Symptoms

The patient is unwell, febrile, loses weight and suffers from abdominal pain and aching limbs. Specific symptoms and signs are related to the organs involved.

Morphology

Nodules (Fig. 18.73) and ulcers (Fig. 18.74), usually 0.5–1.5 cm in size, occur along the course of superficial arteries often on the lower leg. They

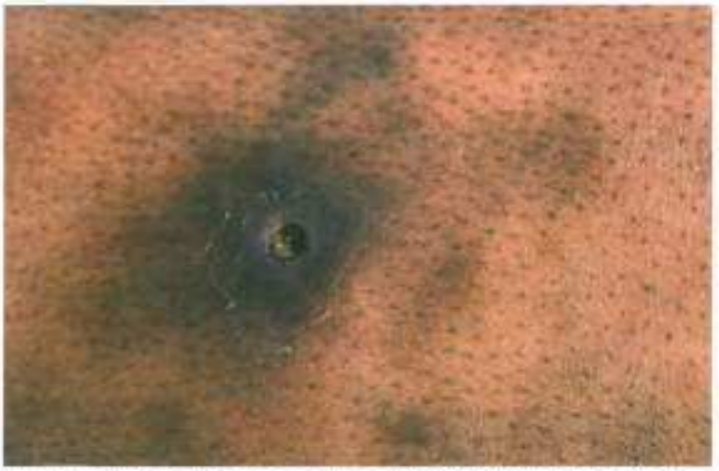


Fig. 18.73 Polyarteritis nodosa. This is a multisystem necrotizing arteritis of small and medium-sized vessels. Nodules occur along the course of cutaneous arteries, particularly on the legs.

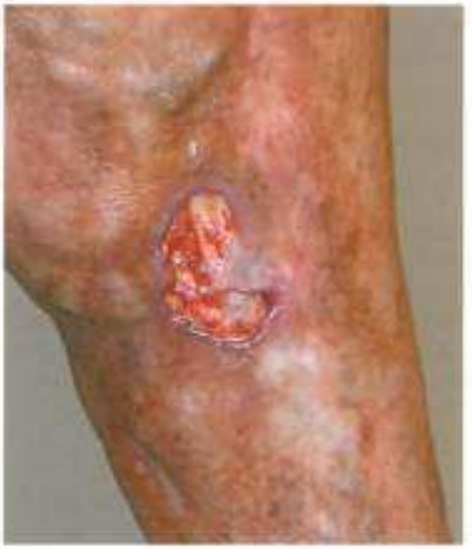


Fig. 18.74 Polyarteritis nodosa. Painful subcutaneous nodules break down into deep ulcers secondary to involvement of medium-sized arteries. (With permission from Bolognia JL, Jorizzo JL, Rapini RP, et al: Dermatology, 2nd edition. London: Elsevier, 2008.)

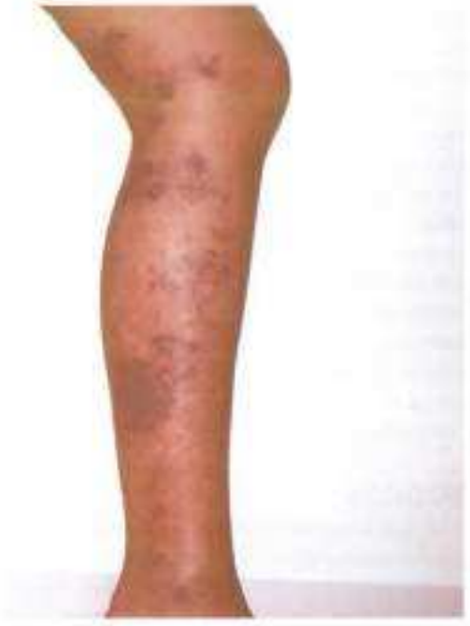


Fig. 18.75 Polyarteritis nodosa. Widespread ecchymoses associated with a livedo reticularis pattern may occur on the legs. (Courtesy of Dr Elisabeth Higgins.)

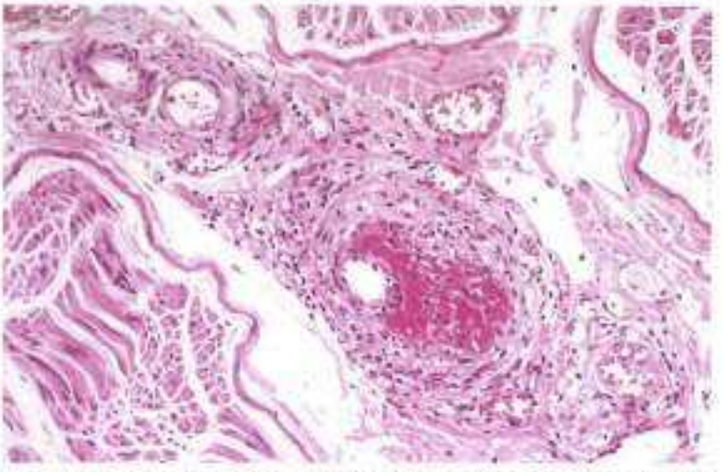


Fig. 18.76 Polyarteritis nodosa. There is intense fibrinoid necrosis of a muscular arteriole adjacent to a small peripheral nerve (left) in the deep subcutaneous fat.

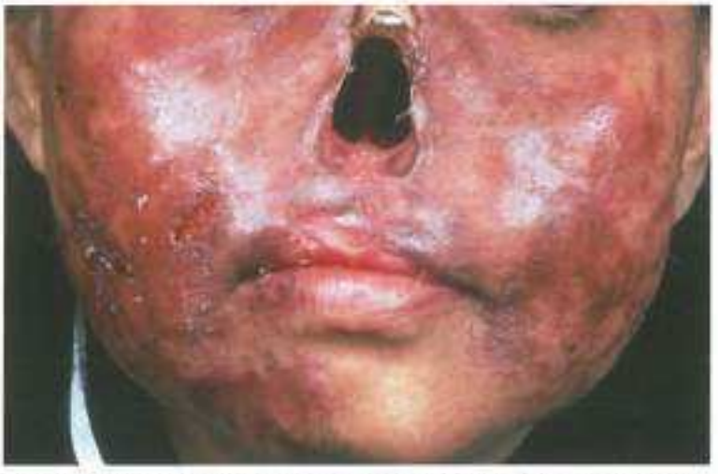


Fig. 18.77 Wegener's granulomatosis. This is a systematic necrotizing arteritic disease involving and destroying the nose and face, lower respiratory tract, other organs and kidneys.

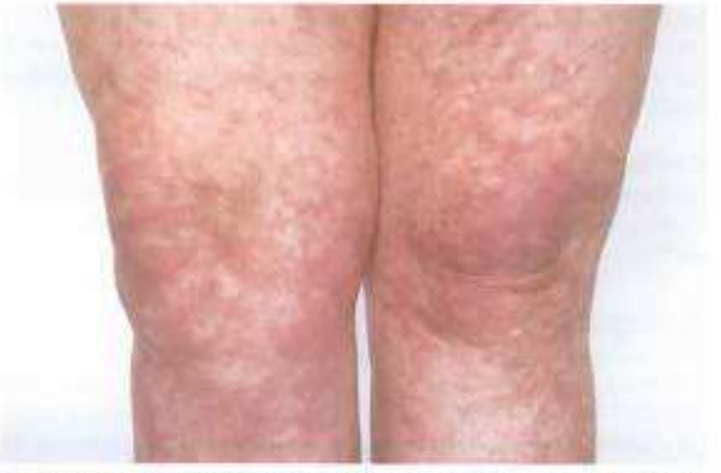


Fig. 18.78 Livedo reticularis with nodules. This is a benign cutaneous form of polyarteritis nodosa. There are recurrent painful nodules, often most appreciated by palpation, associated with livedo reticularis.

are present in about 15%. Livedo reticularis (Fig. 18.75) is present in about 40%. Other cutaneous manifestations include ecchymoses, gangrene and embolic infarcts of the nailfolds and distal aspects of the digits.

Distribution

The nodules occur most often on the lower legs.

Systemic features

The gastrointestinal tract, pancreas, kidney, heart and muscles are most commonly affected. Therefore, gangrene of the bowel, peritonitis, perforation and haemorrhage may occur. Pancreatitis is common. Renal involvement is constant and infarcts are found. Hypertension results. Coronary thrombosis, pericarditis and pericardial haemorrhage are frequent. Mononeuritis multiplex and central nervous system disorders occur as a result of infarction.

Management

Histology either from the skin or another organ is essential for confirming the diagnosis of a necrotizing arteritis (Fig. 18.76). Antineutrophilic cytoplasmic antibodies (ANCA) may be present. Polymorphonuclear leucocytosis, eosinophilia and a high ESR are common. The morbidity and mortality are considerable, particularly from renal and neurological disease and hypertension. Treatment is difficult but systemic steroids are routinely used.

In *Wegener's granulomatosis*, a cytoplasmic ANCA (cANCA)-positive disease, not dissimilar cutaneous features may occur. It is a necrotizing granulomatous disease of the upper (Fig. 18.77) and lower respiratory tract associated with a generalized necrotizing vasculitis of small arteries and veins with a focal necrotizing glomerulonephritis. Purpura and oral ulceration are common, but nodules, pyoderma-like ulcers, pustular eruptions, livedo reticularis, necrotic papules and digital necrosis also occur.

Livedo reticularis with nodules is a benign cutaneous form of polyarteritis nodosa. There are chronically recurring painful eruptions of nodules, mainly on the limbs, associated with livedo reticularis (Fig. 18.78) and often associated with myalgia and sometimes a localized neuropathy. The nodules appear along the line of vessels and the histology is that of a necrotizing vasculitis at the junction of the dermis and the subcutis.

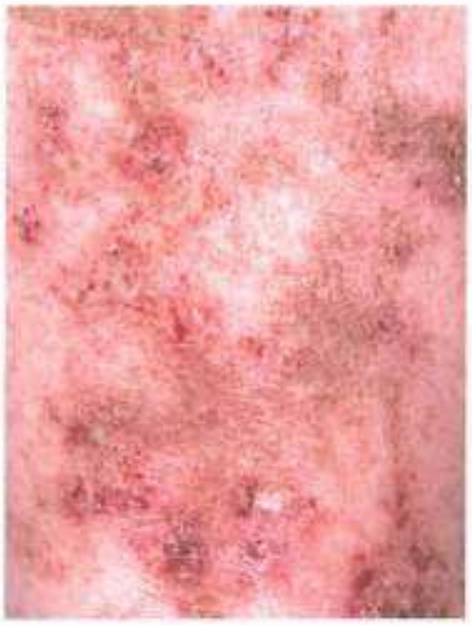


Fig. 18.79 Livedoid vasculopathy. There are focal, painful, purpuric lesions, which ulcerate and heal with stellate atrophic scars, with livedo reticularis.

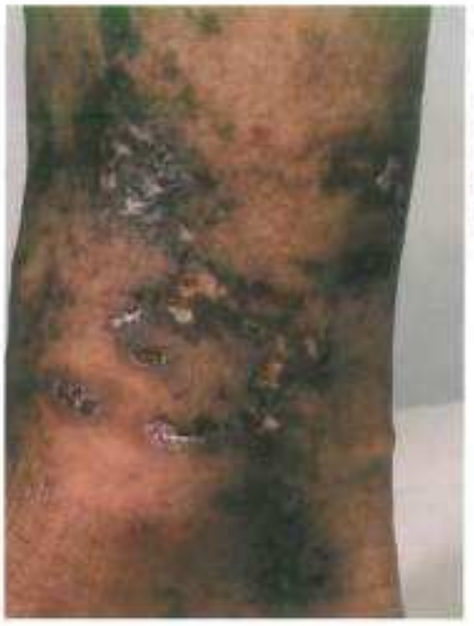


Fig. 18.80 Livedoid vasculopathy. The focal painful purpuric lesions usually ulcerate and slowly heal producing stellate white scars. There is a net-like patterning made by these lesions. He improved greatly with support stockings.

Livedoid vasculopathy

A rare segmental hyalinizing vasculopathy of unknown aetiology causing painful purpuric ulcers with atrophie blanche associated with a reticulate patterning of the extremities, particularly in young women.

Aetiology

Also known as *livedo reticularis with ulceration*, it has a distinctive histology of segmental hyalinization, endothelial swelling and thrombosis, of small and medium-sized blood vessels of the lower limbs with a variable number of perivascular lymphocytes but no evidence of vasculitis. The condition may be idiopathic or secondary to venous hypertension or factors involved in veno-occlusive disease (Factor V Leiden, antiphospholipid syndrome and hyperhomocystinaemia).

Clinical Features

Symptoms

Painful ulcers with mottling of the skin.

Morphology

There are focal painful purpuric lesions (Fig. 18.79) that frequently ulcerate (Fig. 18.80) and only slowly heal to produce white stellate atrophic scars (Fig. 18.81; *atrophie blanche*) with telangiectasia. There is a reticular patterning (livedo-like) of the skin.

Distribution

The legs are affected.

Management

Livedoid vasculopathy needs to be distinguished from other causes of atrophie blanche and livedo reticularis.

Atrophie blanche is a descriptive morphological term and may be seen as part of the cutaneous complications of connective tissue disorders such as SLE, scleroderma, antiphospholipid-antibody syndrome, polyarteritis nodosa, livedoid vasculopathy and venous stasis.

Livedo reticularis is a mottled mauve reticulate (net-like) patterning of the skin. It is common in adolescence as a normal physiological reaction to cold, but the pathological causes are as follows:

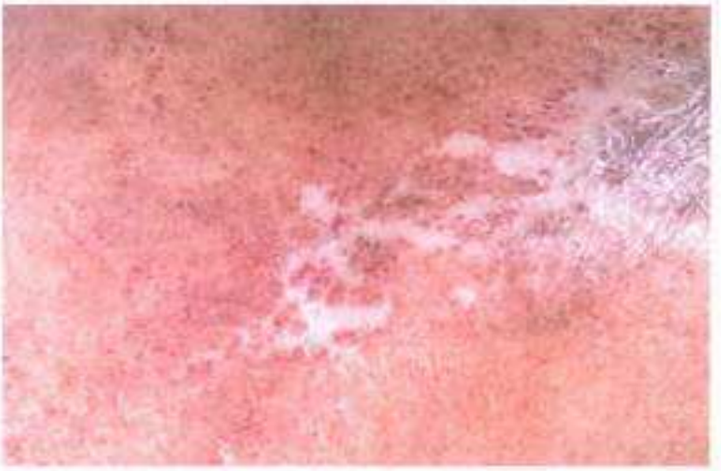


Fig. 18.81 Atrophie blanche. There are stellate atrophic white scars with surface telangiectasia. It occurs with venous stasis but also in connective tissue disorders and livedoid vasculopathy.

- **Haematological (hyperviscosity states)** Antiphospholipid-antibody syndrome, Sneddon's syndrome, cryoglobulinaemia, cryptofibrinogenaemia (often secondary to hepatitis C), myeloma and myeloproliferative disorders
- **Rheumatological** Vasculitis (polyarteritis nodosa, Wegener's, Churg-Strauss), connective tissue disorders and livedoid vasculopathy
- **Cardiovascular (embolic disease)** Cholesterol, septic and atrial myxoma emboli
- **Malignancy** Renal and intravascular lymphoma
- **Endocrine** Hypothyroidism, pernicious anaemia, phaeochromocytoma and carcinoid syndrome
- **Drugs** Amantadine.

Livedoid vasculopathy is commonly treated with fibrinolytic anticoagulant and antithrombotic therapeutic regimens, which include phenformin, ethinylestradiol, heparin and ticlopidine and aspirin, either with pentoxifylline or dipyridamole. Support stockings may be helpful. It does not respond to therapies for vasculitis.

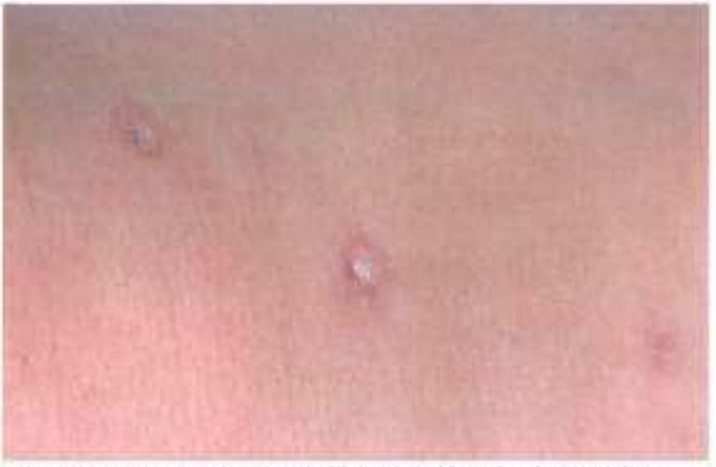


Fig. 18.82 Degos' syndrome. Lesions are usually sparse. The papule leaves behind a grey-white porcelain-like scar.

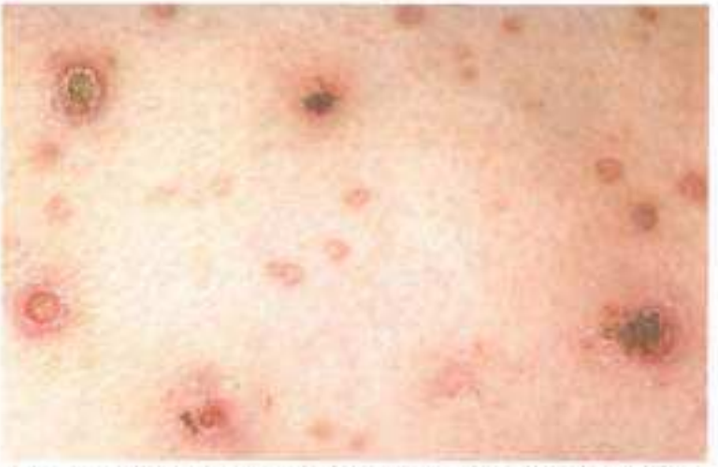


Fig. 18.83 Degos' syndrome. The lesion starts as a red or pink, dome-shaped papule, which develops a central area of necrosis and ends as a small porcelain-like scar. It is a rare vaso-occlusive disorder.

Degos' syndrome (Malignant atrophic papulosis)

A rare endovasculitis that produces characteristic papules in the skin, which may be followed by fatal involvement of the gut, central nervous system and other organs.

Aetiology

It is three times more common in Caucasian males than females and rare in black skins. The histology shows endovascular inflammation, proliferation and thickening of the deep dermal vessels with thrombosis. The cause is unknown.

Clinical Features

Symptoms

The lesions may be slightly pruritic.

Morphology

The lesions are usually sparse and begin as a red or pink, dome-shaped papule (Fig. 18.82) frequently surrounded by a pink, oedematous ring. The papule develops a central area of necrosis. This leaves behind a grey-white porcelain-like colour (Fig. 18.83). Scarring is the final result.

Distribution

The lesions occur in crops over several months or years anywhere on the skin except the face, palms and soles. The genitalia may be involved.

Systemic features

The endovasculitis of the gut is usually lethal. It begins as colicky abdominal pain, vomiting and enteritis and is followed within a period of time by an acute terminal intestinal crisis caused by haemorrhage, perforation or peritonitis. Occasionally the cerebral vessels are also involved.

Management

The clinical picture is very characteristic, although similar lesions may occur in lupus erythematosus and the antiphospholipid antibody syndrome. A skin biopsy shows a central area of dermal infarction secondary to vasculitis (Fig. 18.84). There is no effective therapy. Not all patients die.

Fig. 18.84 Degos' syndrome. On the left, there is epidermal atrophy. Note the underlying zone of dermal infarction.

Pityriasis lichenoides

Pityriasis lichenoides occurs in two forms, but there is an overlap between them. The acute variety is known as pityriasis lichenoides acuta et varioliformis (PLEVA or Mucha–Habermann's disease). The other is pityriasis lichenoides chronic (PLC). Both are forms of a lymphocytic vasculitis, where there is a perivascular and diffuse lymphocytic and histiocytic infiltrate, which largely obscures the dermo-epidermal junction in PLA and is similar, but less pronounced, in PLC. The majority of cases are benign and reactive, probably to an as yet unidentified infectious agent, but occasionally it may be seen prior to or after successful treatment of a lymphoma. Lymphomatoid papulosis was previously included as a variant but it has a quite different histology and the infiltrate is CD30-positive; however, it too may be associated with lymphoma.

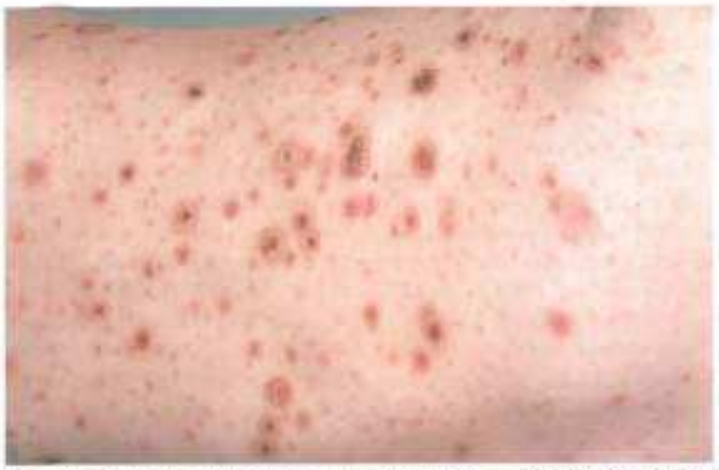


Fig. 18.85 Pityriasis lichenoides acuta et varioliformis. (Mucha-Habermann's disease.) The lesions are at various stages of development. Haemorrhagic and necrotic papules occur, which leave pitted scars and somewhat resemble chickenpox.

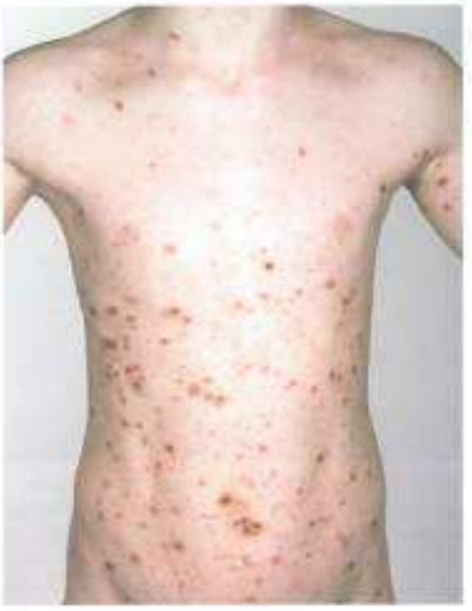


Fig. 18.86 Pityriasis lichenoides acuta. The papules may become vesicular and resemble chickenpox.

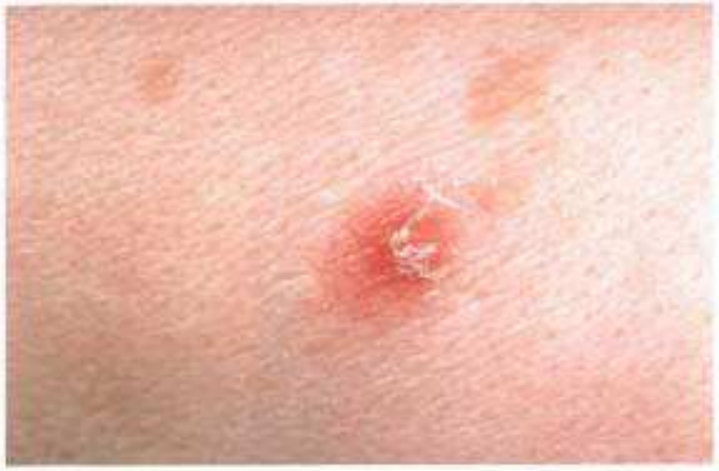


Fig. 18.87 Pityriasis lichenoides chronica. The initial lesion is a purple macule, which rapidly becomes a red-brown papule that develops a micaceous scale as it involutes.

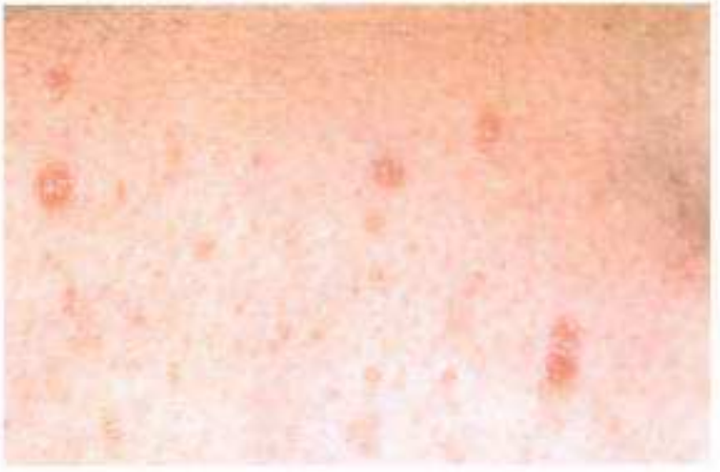


Fig. 18.88 Pityriasis lichenoides chronica. The initial lesion is a purple macule, which rapidly becomes a red-brown papule with an adherent scale.

PITYRIASIS LICHENOIDES ACUTA ET VARIOLIFORMIS

An acute, lymphocytic vasculitis, possibly mediated by immune complexes, which produces a characteristic haemorrhagic papular eruption.

Aetiology

The cause is unknown. It is more common in the young.

Clinical Features

Symptoms

There is occasionally a fever and mild constitutional upset.

Morphology

Vesicles and pustules that become haemorrhagic and necrotic (Fig. 18.85), leaving a pitted scar. Some are reminiscent of the lesions seen in chickenpox (Fig. 18.86) (hence varioliformis).

Distribution

The lesions can be quite limited or widespread over the limbs and trunk.

PITYRIASIS LICHENOIDES CHRONICA

A chronic erythematosquamous papular eruption affecting principally the inner aspects of the limbs.

Aetiology

The disorder affects children and young adults. There are no associated symptoms, although sometimes there may be an antecedent mild fever and malaise. Circulating immune complexes are present and immunoglobulins and complement have been found in the blood vessel walls of affected skin. It is possibly initiated by a virus.

Clinical Features

Symptoms

The lesions are usually asymptomatic.

Morphology

The initial lesion is a purple macule that rapidly becomes a red-brown papule. As it flattens, it develops an adherent scale (Fig. 18.87) and becomes somewhat pink. Postinflammatory hyperpigmentation may occur. The lesions coexist at different stages of development (Fig. 18.88).

Fig. 18.89 Pityriasis lichenoides chronica. The condition is not uncommon in black skins. Although deeply pigmented papules are visible, many of the lesions are hypopigmented and scaly. The pigmentary changes may persist for many years.

Distribution

Mainly the inner aspects of the limbs (Fig. 18.90), but sometimes the trunk (Figs 18.89 and 18.91).

Management

An attack of pityriasis lichenoides acuta may last 1 or 2 months and the patient may have several episodes over a number of years. The disease overlaps with pityriasis lichenoides chronica in that similar lesions occur in both conditions. The histology (Fig. 18.92) varies with the stage of the reaction but the dermal capillaries are surrounded and infiltrated by small lymphocytes, and there is proliferation of their endothelium. The epidermis is oedematous and invaded by lymphocytes and red cells.

Chickenpox can be differentiated since it is an acute vesicular eruption of short duration with oral involvement and fever. PCR and viral culture should be positive.

The clinical picture of pityriasis lichenoides chronica is sufficiently distinctive for a clinical diagnosis to be made. The histology shows a lymphocytic infiltrate that surrounds and sometimes involves small blood vessels, causing vascular damage. There is parakeratosis and an acanthotic epidermis with spongiosis (Fig. 18.93). It needs to be distinguished from

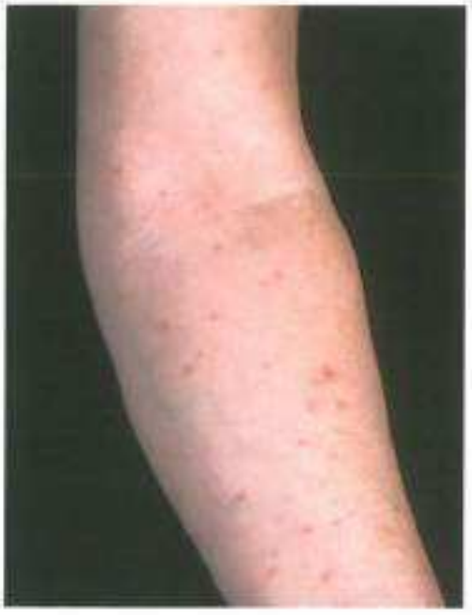


Fig. 18.90 Pityriasis lichenoides chronica. Many small, scattered macules and papules occur more or less symmetrically on the limbs.

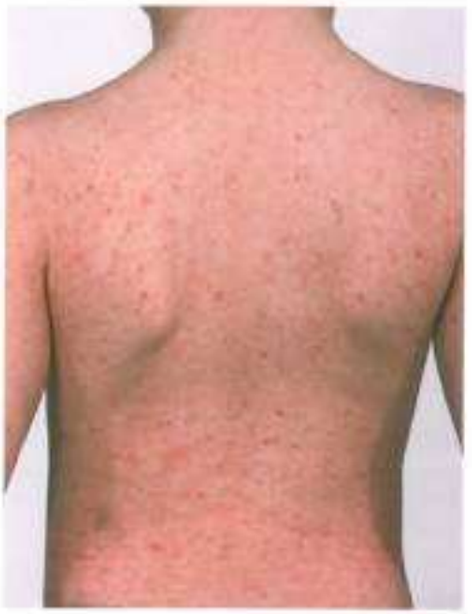


Fig. 18.91 Pityriasis lichenoides chronica. The condition occurs in children as well as young adults. There are many discrete small macules and papules at different stages of development.

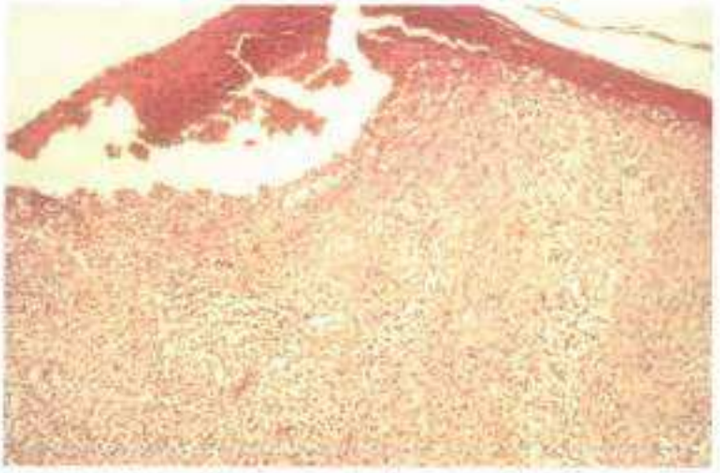


Fig. 18.92 Pityriasis lichenoides acuta. This biopsy comes from the edge of an ulcerated lesion. Note the intense inflammatory cell infiltrate. The adjacent epidermis shows spongiosis and purpura.

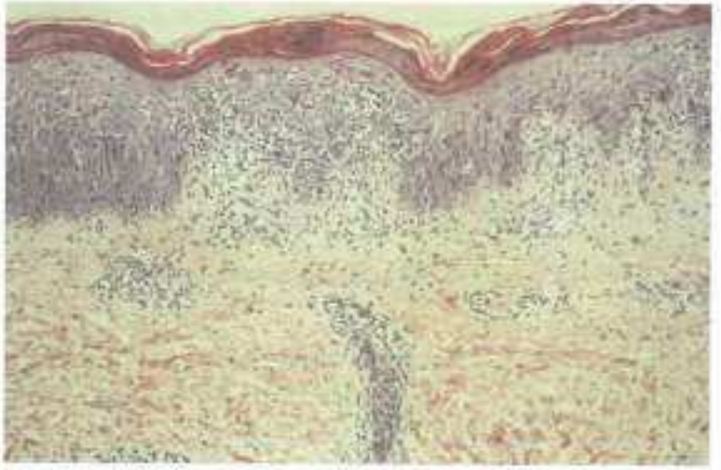


Fig. 18.93 Pityriasis lichenoides chronica. There is parakeratosis with focal acanthosis. Degenerate, eosinophilic keratinocytes are present high in the epidermis and a perivascular, chronic, inflammatory cell infiltrate in the superficial dermis.

guttate psoriasis, in which the lesions are more uniform, have a thick scale and occur particularly on the trunk, and from lichen planus, where the lesions are purple, flat topped and very itchy. Secondary syphilis is probably the most important differential diagnosis, but the palms and soles are usually involved in syphilis and the patient is unwell; serology will distinguish the two.

The disorder is chronic, although it may go into remission after a number of years. It may temporarily disappear with ultraviolet light irradiation including PUVA and occasionally with a 3 week course of an antibiotic such as erythromycin. Methotrexate may be used in troublesome cases, particularly in black skins, where postinflammatory pigmentation may be marked. Attacks of pityriasis lichenoides acuta are short-lived and treatment is often unnecessary, but methotrexate may be required in the febrile ulceronecrotic variant.

Papular acrodermatitis of childhood

A rare, short-lived, monomorphic eruption of the limbs and face that occurs in childhood, sometimes associated with lymphadenopathy.

Aetiology

Known as the *Gianotti–Crosti syndrome* and described in 1955, all the affected children were infected with hepatitis B. Subsequently other viruses (Epstein–Barr, Coxsackievirus, HIV and cytomegalovirus) have been implicated. However, often no cause is found. It is not a vasculitis but an infiltrate of lymphocytes and histiocytes around dilated capillaries in an oedematous upper dermis. There may be some acanthosis and hyperkeratosis. It is likely to be a reactive process.

Clinical Features

Symptoms

The child is usually remarkably well.

Morphology

A profuse monomorphic eruption of deep red papules (Figs 18.94 and 18.95) develops over a space of a few days.

Distribution

Lesions first occur on the buttocks, thighs and legs (Fig. 18.96) and spread to the arms and face. The trunk is frequently spared (Fig. 18.97).

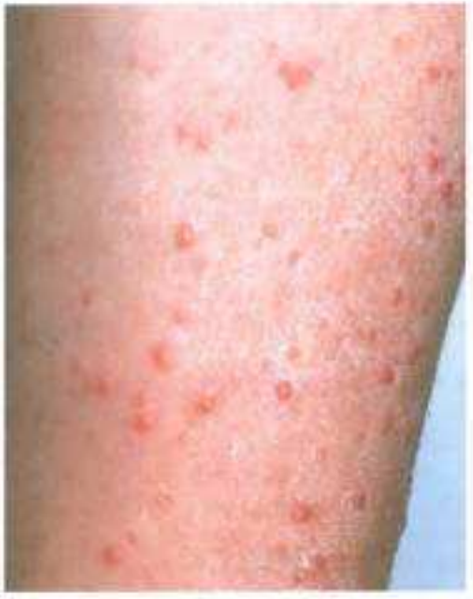


Fig. 18.94 Papular acrodermatitis of childhood. The papules are monomorphic and have a deep red colour, as in this 3-year-old child.

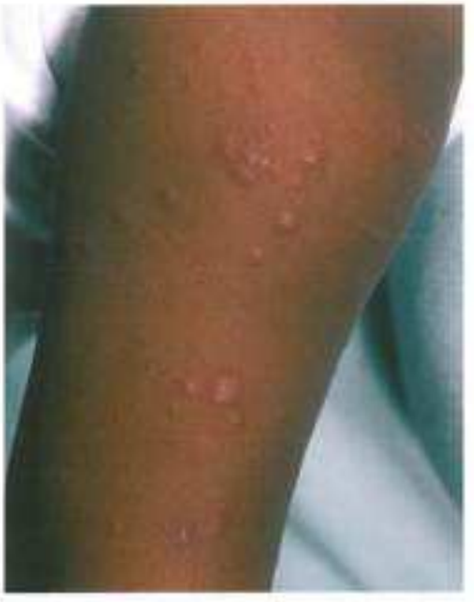


Fig. 18.95 Papular acrodermatitis of childhood. There are red-brown papules, which are essentially similar to each other. They erupt abruptly on the limbs and resolve within a few weeks.

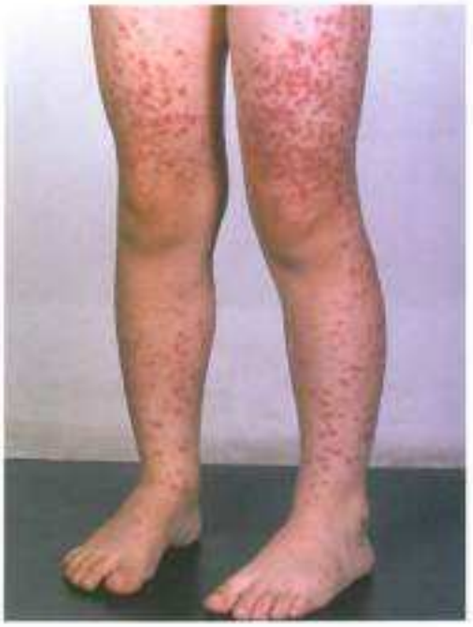


Fig. 18.96 Papular acrodermatitis of childhood. A profuse monomorphic eruption of deep-red papules occurs over the limbs.

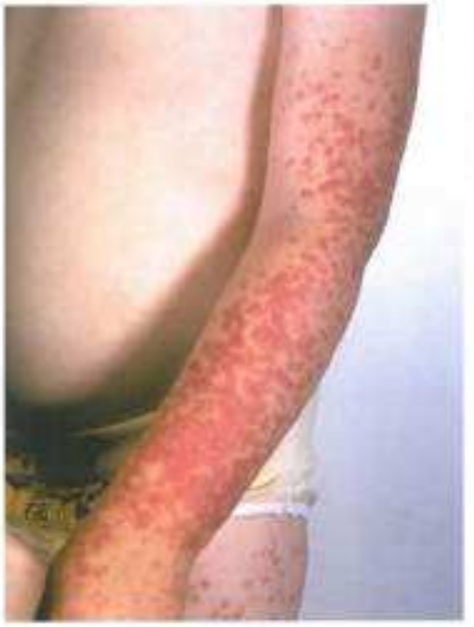


Fig. 18.97 Papular acrodermatitis of childhood. The limbs are involved but the trunk is usually spared. These photographs show the same child as in Fig. 18.96.

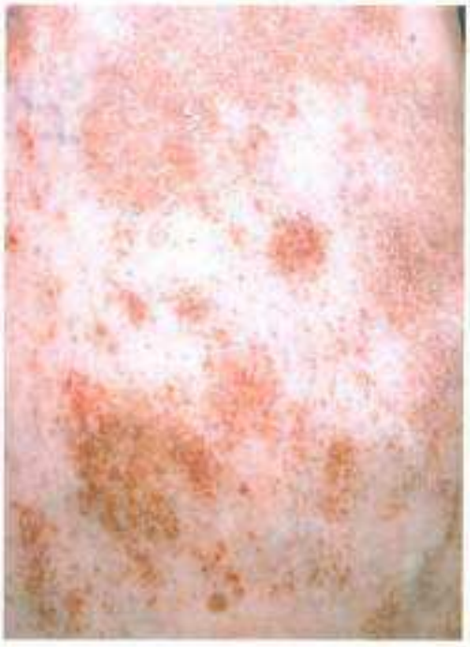


Fig. 18.98 Capillaritis. Increased venous pressure and stasis are responsible for some cases. Varicosities are evident in addition to the brown patch.

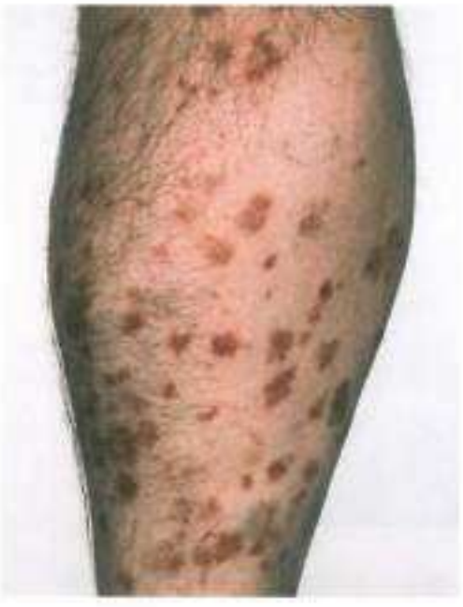


Fig. 18.99 Capillaritis. Some of the lesions are purpuric secondary to leakage of erythrocytes into the dermis. These ultimately are phagocytosed, but the iron left behind leaves a characteristic orange-brown staining of the skin.

Systemic features

There may be generalized lymphadenopathy.

Management

A skin biopsy may be helpful. Liver function tests and screening tests for hepatitis and other viruses are useful. There is no treatment for asymptomatic patients and the condition resolves within a few weeks.

Capillaritis (Pigmented purpuric eruptions)

A collection of chronic disorders that simulate bruising, characterized by a perivascular lymphocytic infiltrate with endothelial swelling and consequent extravasation of red cells and subsequent haemosiderin deposition in macrophages.

Aetiology

These disorders have a bewildering nomenclature. Their cause is often obscure although gravity and increased venous pressure may be responsible for some and eczema for others. Morphologically similar eruptions have occurred secondary to drugs (carbromal, aspirin, paracetamol, thiamine and meprobamate) and clothing (khaki uniforms). Gravitational purpura is very similar.

Clinical Features

- **Schamberg's disease (progressive pigmented purpura)** More common in males, it consists of irregular bruise-like patches of orange-brown discoloration with tiny petechiae (cayenne pepper spots) within them (Fig. 18.98), occuring predominantly on the limbs (Fig. 18.99) but sometimes elsewhere. They are remarkably chronic, although spontaneous cure does occur. A more acute short-lived pruritic condition of the lower legs and lower body is known as *itching purpura* (eczema-like purpura, *Doucas and Kapetonakis disease*) but its distinction from Schamberg's disease may be artificial.
- **Pigmented purpuric lichenoid dermatosis of Gougerot and Blum** Lichenoid papules occur in addition to the changes described in Schamberg's disease. It may well represent the same condition.
- **Lichen aureus** This is a localized rust-coloured solitary lesion (Fig. 18.100) that may persist for years and resembles a bruise. The petechiae are slightly raised and lichenoid.
- **Purpura annularis telangiectoides (Majocchi's disease)** The lesions are annular and 1–3 cm in diameter. They occur in adolescence or early adult life in either sex. They may be quite limited or numerous. They are not associated with venous stasis. They tend to persist.

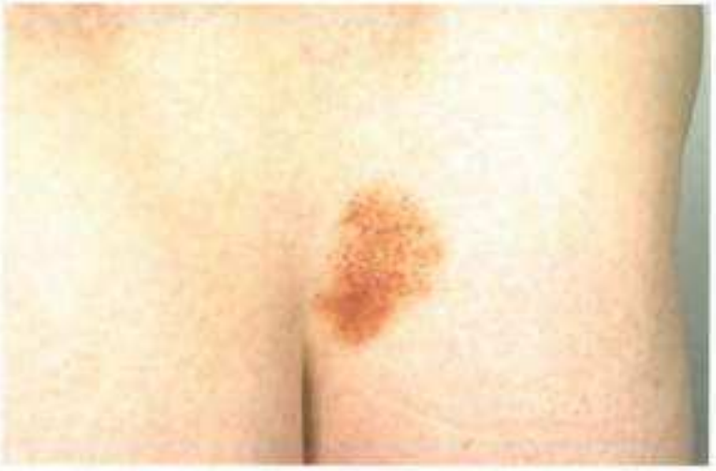


Fig. 18.100 Lichen aureus. The earliest petechiae are purple, but they become brown as a result of haemosiderin deposition.

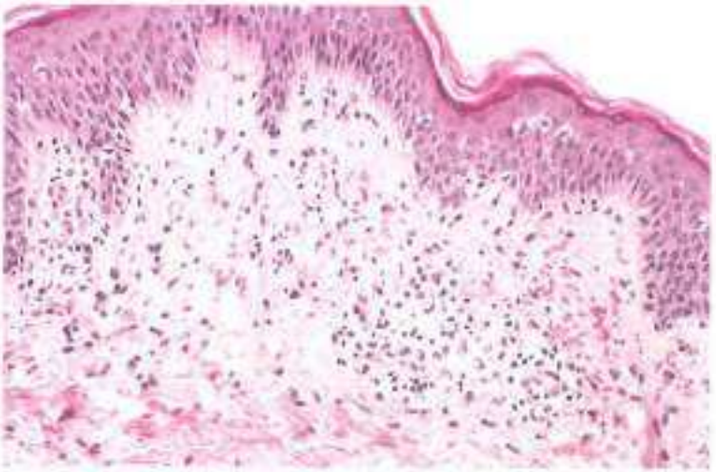


Fig. 18.101 Lymphocytic capillaritis. In the papillary dermis, slightly dilated capillaries are surrounded by a predominantly lymphocytic infiltrate. Free red cells (purpura) are conspicuous in the adjacent, rather oedematous connective tissue.

Management

Histologically, there is a perivascular and interstitial inflammatory infiltrate of T cells, Langerhans' cells and macrophages, with extravasation of red blood cells and haemosiderin deposition (Fig. 18.101). Increased expression of adhesion molecules in endothelial cells suggests that the condition is a T cell-mediated immune response, particularly when related to drugs.

Potent topical glucocorticosteroids may help some patients, especially those with itching. Management of venous stasis and support stockings may be helpful where this is relevant.

Fixed drug eruption

A fixed drug eruption is the occurrence of a red-brown swelling in an identical site each time a particular drug is ingested.

Aetiology

The mechanism for this remarkable phenomenon is obscure. It erupts 1–2 weeks after the first exposure to the drug and subsequently within 24 hours. The main offenders are laxatives (especially phenolphthalein), barbiturates, non-steroidal anti-inflammatories, sulphonamides, tetracyclines, griseofulvin, phenacetin, oral contraceptives, phenylbutazone, carbamazepine and phenytoin.

Histologically in the acute stages, there are similarities to erythema multiforme with loss of the cell outlines and necrosis of the lower epidermis. In less active lesions, the epidermis is relatively normal but the dermis is oedematous and there is an obvious perivascular lymphocytic infiltrate. Subsequently, there is an increase in melanin in the epidermis and within the melanophages of the dermis. The common presentation is very distinctive. In multiple bullous reactions the lesions resemble a localized toxic epidermal necrolysis.

Clinical Features

Symptoms

The disorder recurs in the same site every time.

Morphology

Single or multiple, round or oval, well-defined, red-brown (Fig. 18.102), oedematous plaques are followed by hyperpigmentation (Fig. 18.103). Diffuse hypermelanosis is sometimes seen in black-skinned patients (Fig. 18.104). Very occasionally, a more generalized bullous fixed drug eruption (Fig. 18.105) with subsequent sheeting off of the skin occurs.

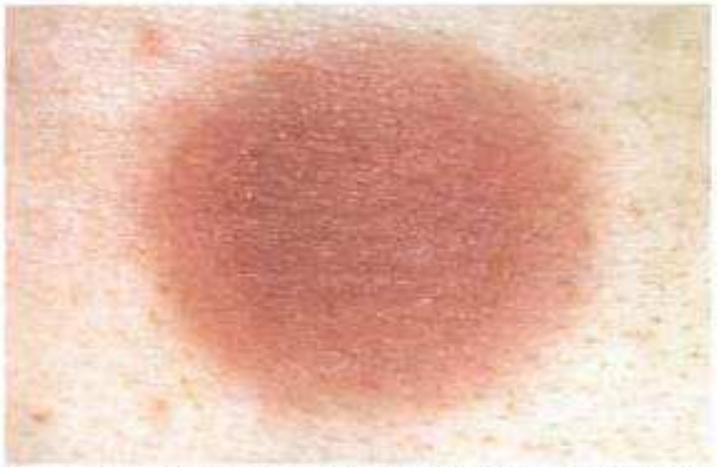


Fig. 18.102 Fixed drug eruption. The lesion is well defined, reddish-brown and oedematous. It recurs in the same site each time the allergen is ingested.

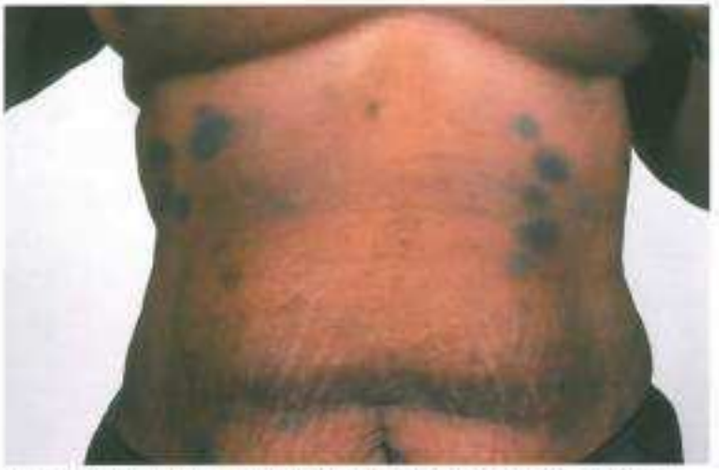


Fig. 18.103 Fixed drug eruption. As the acute reaction subsides, a round macular area of hyperpigmentation remains for a long time. If the cause remains undetected, multiple areas occur.

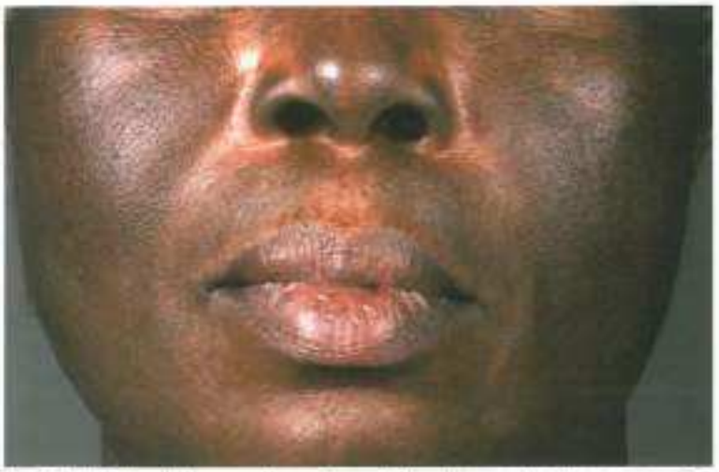


Fig. 18.104 Fixed drug eruption. A more diffuse hypermelanosis may occur in black skins. The commonest cause is laxatives.

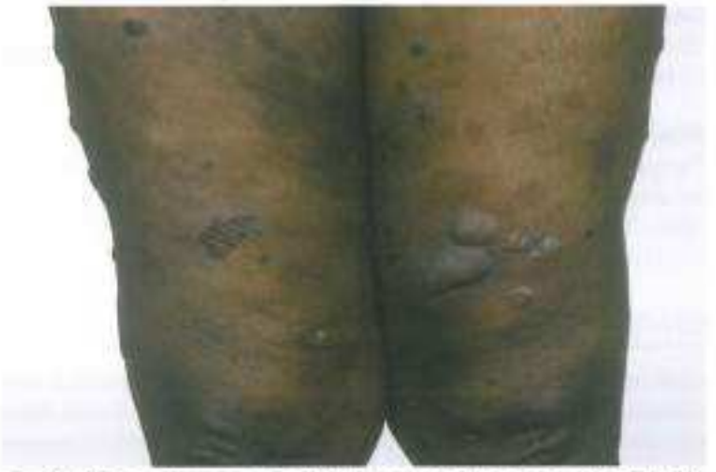


Fig. 18.105 Fixed drug eruption. This more generalized type may be a localized form of toxic epidermal necrolysis. This was caused by phenytoin.

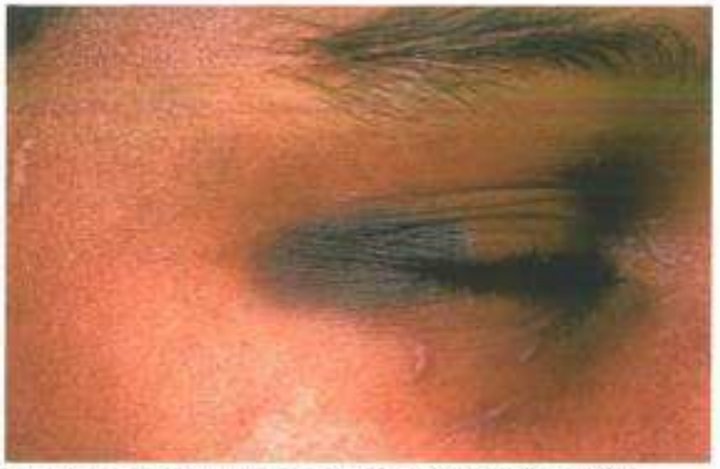


Fig. 18.106 Fixed drug eruption. The face is a common site. Fixed drug eruptions may occur in children.

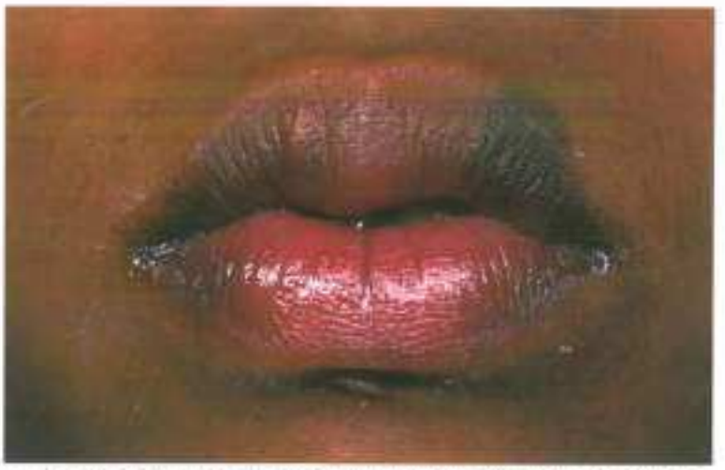


Fig. 18.107 Fixed drug eruption. Round macules of pigment are characteristic of the postinflammatory change following the reaction. It recurs in the same site each time the drug is ingested.

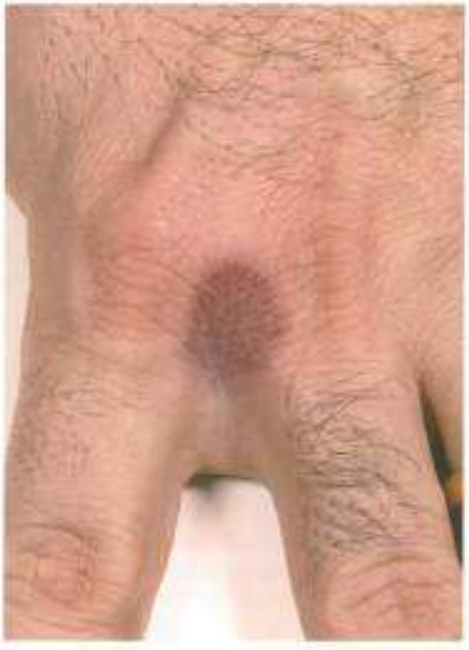


Fig. 18.108 Fixed drug eruption. The back of the hand is a characteristic site. The condition recurs in the same place each time the drug is ingested.

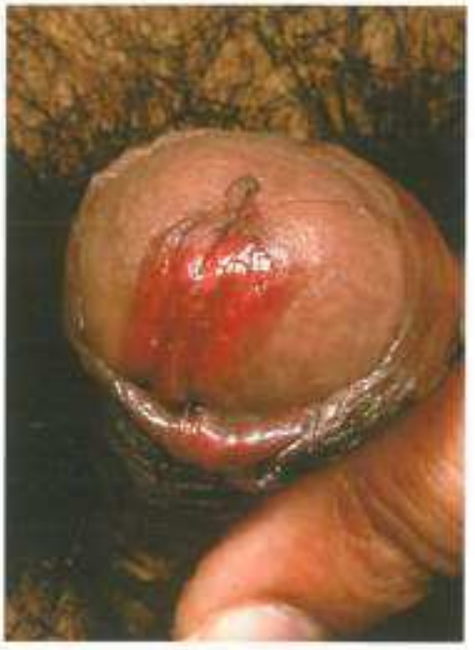


Fig. 18.109 Fixed drug eruption. The lesion may become bullous and erosive. The glans penis is a common site.

Distribution

The areas most affected are the face (Fig. 18.106), lip (Fig. 18.107), mouth, backs of the hands (Fig. 18.108), genitalia (Fig. 18.109) and limbs.

Management

The lesion develops within a few hours and subsides fairly rapidly once the drug is withdrawn. The condition is reproducible if the drug is given again. It may be quite difficult to identify because the patient may not accept the explanation, particularly in the case of laxatives.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a reaction between viable immunocompetent donor cells and the recipient following marrow or solid organ transplantation or blood product transfusion resulting in cutaneous, ocular, pulmonary, gastrointestinal and hepatic abnormalities.

Aetiology

GVHD complicates 70% of allogeneic bone marrow transplants for leukaemia, lymphoma, aplastic anaemia, genetic immunodeficiencies or inborn errors of metabolism, despite the use of HLA-matched sibling donors and immunosuppressive agents.

Blood product transfusion (where non-irradiated blood products contain viable immunological cells) and solid organ transplantation (where passenger leucocytes are transplanted with the organ) are other causes. In immunodeficient neonates, immune cells are transferred from the mother during gestation because the normal fetal allograft rejection mechanisms have failed. These are usually intact before the fifth month of gestation and do not permit engraftment of maternal leucocytes. GVHD is more common in older subjects, males given female donors, with concomitant cytomegalovirus infections and donor lymphocyte infusions (which particularly cause lichen planus-like eruptions and scleroderma).

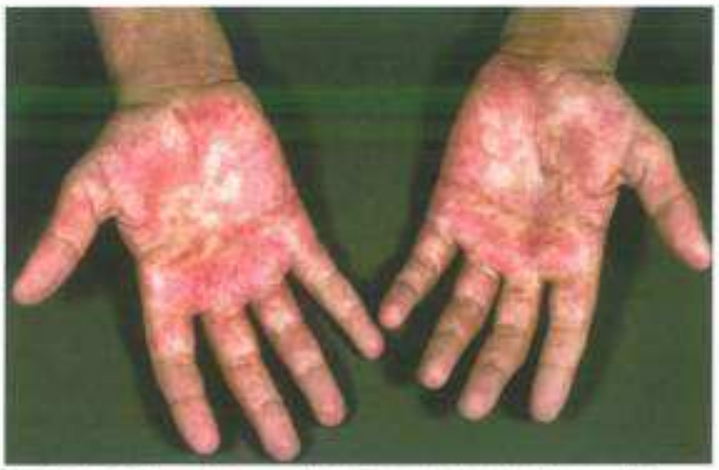


Fig. 18.110 Acute graft-versus-host disease. A maculopapular eruption occurs on the palms and soles. There may be diarrhoea from gastrointestinal GVHD and abnormal liver function.

Fig. 18.111 Acute graft-versus-host disease. The lesions may become more lichenoid, with purple papules. Lichenoid graft-versus-host disease is particularly seen in patients who have received donor lymphocyte infusions.

Based on the time of onset of the eruption after the transplant, GVHD has been subdivided into acute before 100 days or chronic after the transplant. This is less accepted now and there is an erythrodermic ichthyosiform or eczematous variant, particularly associated with reduced-intensity matched unrelated donor transplant with Campath conditioning, which can come on at any time.

Clinical Features of Acute Disease

Symptoms

Painful or itchy spots appear 7 to 21 days after the graft.

Morphology

The eruption is a maculopapular morbilliform exanthem with perifollicular papules. The macules coalesce into patches or plaques and subsequently desquamate and there is postinflammatory hyperpigmentation. In more severe cases, there are blisters and generalized erythroderma and a resemblance to toxic epidermal necrolysis. The eruption can be graded from 1 to 4, with the most severe being associated with a poor prognosis.

Distribution

The eruption is acral with involvement of the palms (Fig. 18.110) and soles. There is a violaceous discoloration of the ears and initially the cheeks or the sides of the neck and upper back are involved.

Systemic features

There is a fever initially and the gastrointestinal tract may be involved with nausea, vomiting and abdominal pain; often there is a voluminous bloody diarrhoea. The small intrahepatic bile ducts are involved, with right upper quadrant abdominal tenderness and pain, and there may be cholestatic jaundice. Serum levels of liver enzymes are raised.

Clinical Features of Chronic Disease

Symptoms

Chronic GVHD usually occurs about 4 months after the transplant but may occur earlier. The mouth is involved in most patients as well as the skin.

Morphology

The acute rash may continue after a disease-free interval or may become lichenoid (Fig. 18.111) which may lead to hyperpigmentation (Fig. 18.112), sclerodermatous, ichthyotic or eczematous (Fig. 18.113).

Fig. 18.112 Lichenoid graft-versus-host disease. Just like ordinary lichen planus, postinflammatory pigmentation may be severe, particularly in Asian skins.

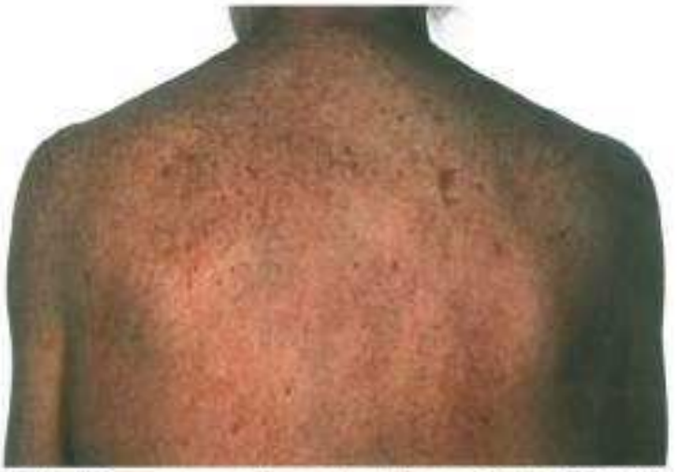


Fig. 18.113 Eczematous graft-versus-host disease. The whole integument may be involved, as in erythroderma. The patient loses heat and fluid and is ill, shivering and miserable. The gut and liver are often involved.

Fig. 18.114 Eczematous graft-versus-host disease. The appearance is eczema, but the histology is that of eczema and graft-versus-host disease. It is common following reduced conditioning (with Campath) allograft stem cell transplantation.

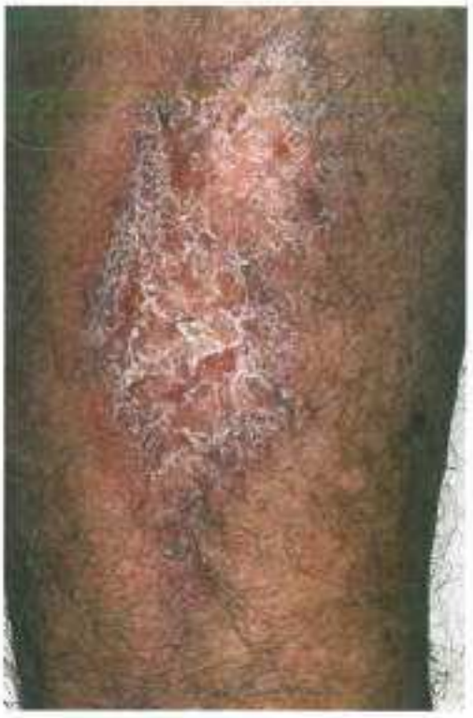


Fig. 18.115 Localized sclerodermatous graft-versus-host disease. Localized patches occur simulating morphoea. It may respond to PUVA.

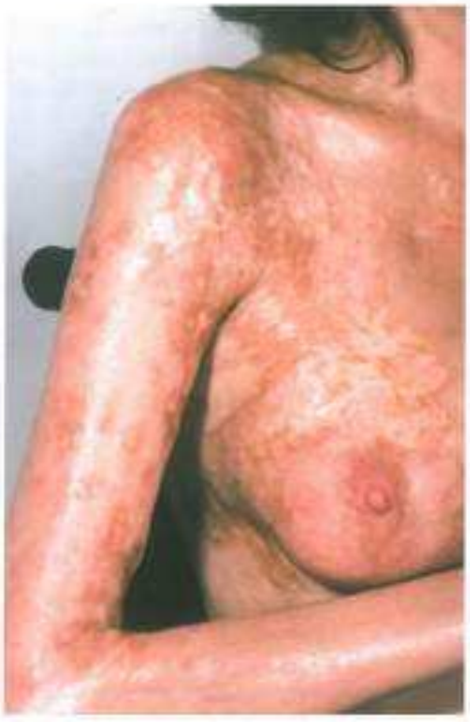


Fig. 18.116 Sclerodermatous graft-versus-host disease. These severe cases with contractures are now fortunately rare. She was free of her acute myeloid leukaemia for 9 years before the original clone returned, possibly due to immunosuppression required to treat the graft-versus-host disease.

Distribution

The eczematous type (Fig. 18.114) becomes universal. The lichenoid eruption particularly affects the palms and soles and has atypical features both in distribution and in that the lesions are less sharply angulated than ordinary lichen planus. Periorbital areas and ears may be affected. Occasionally the eruption is dermatomal, simulating herpes zoster.

The sclerotic type may be localized (Fig. 18.115) or become quite generalized and disabling, with ulcers occurring on the legs and fibrosis over ligaments and joints leading to contractures (Fig. 18.116) and restrictive entrapment of nerves. There is generalized wasting and this form of sclerodermatous chronic GVHD rarely remits. There may be alopecia and nail changes (Fig. 18.117).

The oral changes affect the tongue, palate and lips. There is a diffuse or focal enhanced redness of the mucosa, with atrophy and loss of the lingual papillae and a lichenoid reticular or papular hyperkeratotic pattern on the mucosa. The mouth is dry.

Systemic features

The extracutaneous features of chronic GVHD mimic connective tissue diseases such as lupus erythematosus and there is involvement of the gastrointestinal tract, liver, lungs, the lymphoreticular systems and the musculoskeletal systems.

Histology

In acute GVHD, the epidermis is damaged (Fig. 18.118). There is basal cell hydropic degeneration and necrotic eosinophilic keratinocytes (apoptotic cells) are scattered throughout, associated with adjacent lymphocytes. There is dermal oedema, dilated blood vessels and a perivascular lymphocytic infiltrate. The changes may be more marked with subepidermal bullae and more dyskeratotic cells and keratinocyte necrosis. In chronic GVHD of the lichenoid variety, the appearances are quite similar to lichen planus. There is epidermal atrophy and dermal fibrosis in the sclerodermoid type.

Management

The clinical appearances are fairly characteristic and an important indication of rejection. However, in acute GVHD, other conditions to bear in mind are radiation recall phenomena, drug-induced acral erythema or neutrophilic eccrine hidradenitis, viral exanthems and the eruption of leucocyte recovery. The last may occur after autologous marrow transplantation or intensive chemotherapy without transplantation and follows profound peripheral leucopenia followed by leucocyte recovery.

The prime object is to prevent GVHD by optimal recipient donor matching and pharmaco-prophylaxis, but acute GVHD should be treated with systemic steroids, ciclosporin or mycophenolate mofetil. The treatment of chronic GVHD is not satisfactory. Steroids with or without ciclosporin are employed with prophylactic antibiotics. Thalidomide has been used, as have retinoids, penicillamine and photochemotherapy including extracorporeal photophoresis.

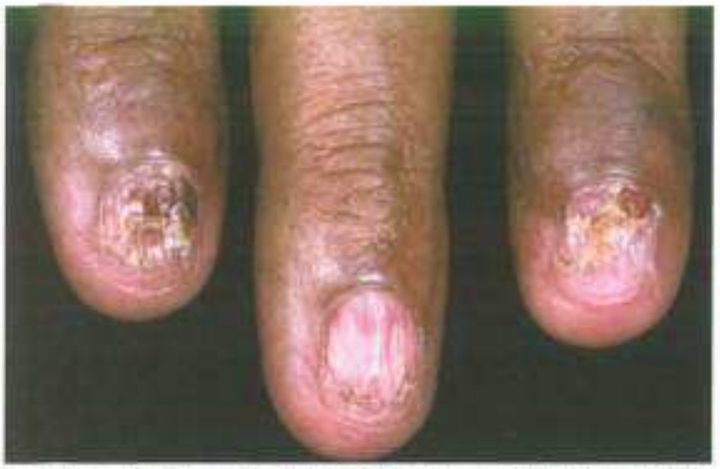


Fig. 18.117 Graft-versus-host disease. The nails may be involved and scarring occurs similar to that seen in lichen planus.

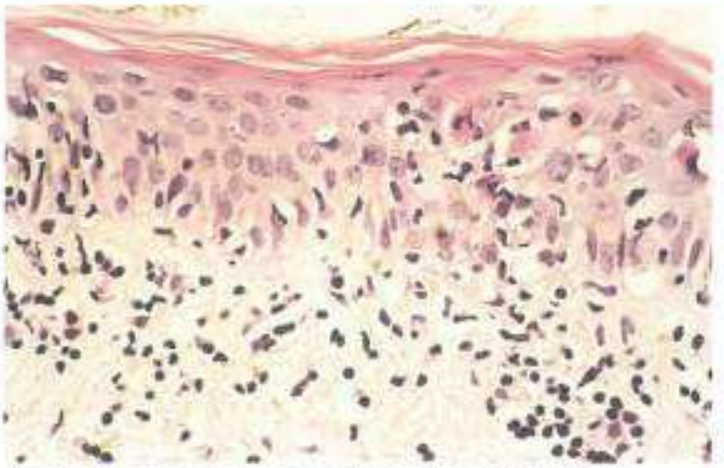


Fig. 18.118 Acute graft-versus-host disease. The epidermis shows intracellular oedema, intraepidermal lymphocytes, satellite cell necrosis and cytoid body formation.

Drug eruptions

Drug eruptions are common. It is important to know what drugs a patient has taken in the weeks preceding the eruption because the patient may have completed the course several days before the eruption appears. This is particularly true of penicillin derivatives. Also, patients do not 'count' as drugs agents that they have purchased from a chemist without prescription (e.g. laxatives and aspirin) nor drugs that they have been taking for a long time. Although drug eruptions are usually related to a recently prescribed medication, this is not always so. Sometimes fairly intense questioning of the patient is required in order to determine what a patient has ingested.

Probably all drugs can cause an eruption on the skin, but clearly some do so more regularly than others. Antibiotics, for example, are high-rate offenders, whereas a rash caused by digoxin must be very uncommon. Sometimes it is difficult to know which drug is responsible because the patient is taking so many, so a list of the likely culprits is helpful. These are:

- **Antibiotics** Penicillin, ampicillin, flucloxacillin, sulphonamides (including co-trimoxazole), trimethoprim, tetracyclines
- **Non-steroidal anti-inflammatory drugs** Phenylbutazone, azapropazone, fenclofenac, salicylates
- **Diuretics** Thiazides, amiloride
- **Drugs affecting the central nervous system** Barbiturates, amitriptyline, phenothiazines, carbamazepine
- **Cardiovascular drugs** Beta-blockers, amiodarone, methyldopa, captopril
- **Rheumatological drugs** Penicillamine, allopurinol, gold
- **Miscellaneous** Sulphonylureas, sulphasalazine.

The scene, however, is always changing as new drugs are introduced. In some cases, the risk is already suspected from clinical trials, but this is not always so. It is important that all reactions to new drugs are monitored and reported to the Committee on Safety of Medicines or its equivalent. There is, unfortunately, no readily available way of testing for drug reactions. Clearly, the definitive test would be to give the patient the drug again in order to see whether the side-effect was reproducible, but this may be dangerous because anaphylaxis or uncontrollable erythroderma may result.

Drug reactions may result from an allergic or non-immunological mechanism. The risk of immunogenicity is greater if the drug molecule is large and complicated. Small-molecular-weight drugs do not produce allergic reactions unless they can form stable covalent bonds with tissue macromolecules, that is, act as a hapten. Even if a drug does elicit an immune response (penicillin, for example, produces antibodies in most patients), only a small number of patients develop a clinical reaction. The route of administration of the drug modifies the nature of the response. Topical applications produce delayed hypersensitivity contact dermatitis; oral or nasal exposure stimulates the secretory immunoglobulins A and E; and intravenous exposure is most likely to induce anaphylaxis. The ability of the host to metabolize the drug is important. Those who acetylate drugs slowly are much more likely to get a lupus-like syndrome with hydralazine than those who do not.

The immunology of allergic cutaneous reactions is not very well understood. The Gel and Coombs hypersensitivity classification has been useful to some extent, but not all rashes can be so classified.

- **IgE-dependent drug reactions (Type I immediate hypersensitivity)** Penicillin is the classic example. Urticaria, angio-oedema and anaphylaxis may result. This is probably the only drug for which it is practical to test sensitivity. Intradermal injection of penicillin produces local wheal and flare within 15 minutes in allergic subjects and RAST testing correlates well with the results of skin tests.
- **Cytotoxic Type II** The antigen attaches to a cell, which is then destroyed by antibodies and complement. This explained the purpura caused by Sedormid, a hypnotic that is no longer available, where the cell affected is the platelet.
- **Immune complex-dependent (Type III)** This results from the drug combining with an antibody to form complexes with complement; these are precipitated out in the blood vessels. Erythema nodosum, vasculitis and serum sickness are examples of this.
- **Cell-mediated (Type IV)** Reactions of this type are seen with topically applied drugs, such as in contact dermatitis.

Non-immunological reactions may occur through activation of an effector pathway. Thus opiates, polymyxin, D-tubocurare and radiocontrast media release mast cell mediators and cause urticaria. Other drugs may activate complement or alter arachidonic acid metabolism, for example aspirin and certain non-steroidal anti-inflammatories, and induce anaphylaxis.

Drugs may be responsible for any of the reactive conditions described in this chapter, such as toxic erythema, urticaria, erythema multiforme and erythema nodosum. Toxic erythema and urticaria are the most common patterns, but some drugs may also stimulate cutaneous disorders, such as lichen planus, acne and psoriasis. The correct diagnosis may be suggested because the eruption is atypical or does not respond to the appropriate therapy for that disease. A discussion of such mimicry follows. Some drugs may produce multiple cutaneous patterns. Gold, for example, may produce

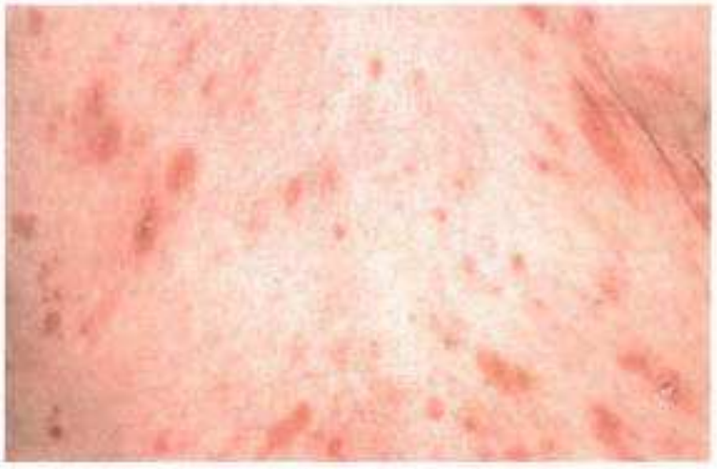


Fig. 18.119 Lichenoid eruption. Gold causes a variety of skin reactions. The histology of this was lichenoid. The mouth, genitalia and palms and soles are often involved, together with the widespread rash.

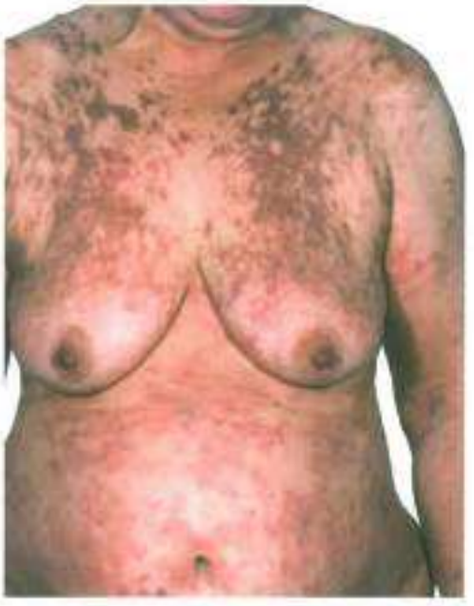


Fig. 18.120 Lichenoid eruption. Drug eruptions may simulate individual skin disorders, but tend to be atypical and this in itself may suggest the cause, in this case isoniazid. The abdomen is covered in purple plaques and the upper chest in postinflammatory pigmentation, a frequent complication of lichenoid eruptions.

a non-specific maculopapular pruritic eruption, a widespread lichenoid eruption, a pityriasis rosea-like rash or an erythroderma with cheilitis and stomatitis. There may, in addition, be eosinophilia, proteinuria and haematological complications including neutropenia, thrombocytopenia and aplastic anaemia. Penicillamine may produce an acute exanthematic rash but also pemphigus and some remarkable elastotic changes. It is a trace metal chelator and causes elastosis by interfering with copper-dependent cross-linkages of elastin and collagen. Cutis laxa, pseudoxanthoma elasticum and elastosis perforans serpiginosa (transepidermal elimination of damaged elastic tissue) may occur.

Types of Drug-induced Eruptions

- **Lichenoid eruptions** These eruptions are similar to but not quite typical of lichen planus, which may suggest the diagnosis. Gold (Fig. 18.119), arsenic, chlorthiazide, phenothiazine, para-aminosalicylic acid, isoniazid (Fig. 18.120) and chloroquine may cause them. There was an epidemic of lichenoid eruptions during World War II when troops were given mepacrine as an antimalarial drug. Penicillamine causes a lichenoid eruption that particularly affects the mucous membranes, especially during the treatment of primary biliary cirrhosis.
- **Acneiform eruptions** The most common drugs that produce acne are the corticosteroids, both topical and systemic. The latter produce an eruption on the face and chest, but it may well spread to the lower abdomen, lower back, upper arms and thighs. The individual lesions consist of monomorphic papules or pustules, while the other features of acne vulgaris, such as comedones, cysts and scars, are not seen. Radioopaque materials, X-ray irradiation, ethambutol, anticonvulsants, dantrolene (Fig. 18.121), isoniazid (Fig. 18.122) and ethionamide are other causes. Iodides and bromides are acnegenic. Occasionally, particularly if the iodides are continued, bullous lesions occur that become haemorrhagic and ultimately develop into vegetating masses studded with pustules, which are extremely disfiguring (*iododerma*).
  Epidermal growth factor receptor (EGFR) inhibitors used in colorectal, breast, pancreatic and non-small cell lung cancers (e.g. gefitinib, erlotinib, and cetuximab) may produce a papulo-pustular acneiform eruption, which is tetracycline responsive. This is because EGFR is also expressed on basal keratinocytes, sebocytes, the outer hair root sheath

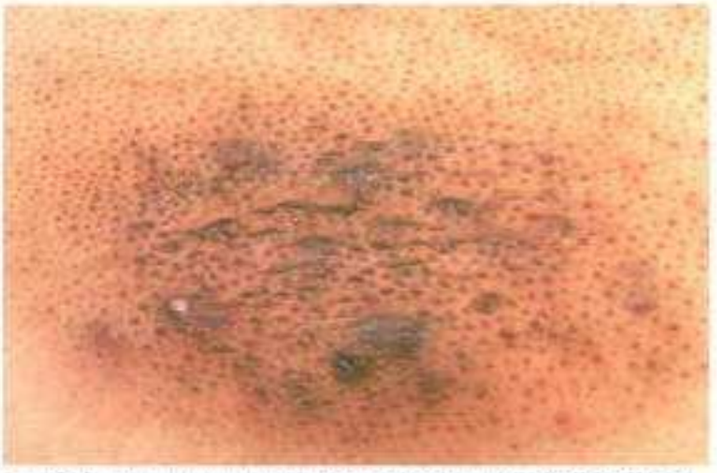


Fig. 18.121 Dantrolene-induced comedone reaction. Dantrolene sodium, a muscle relaxant, is comedogenic and produces a characteristic eruption of blackheads. (Courtesy of Dr Andrew Pembroke.)

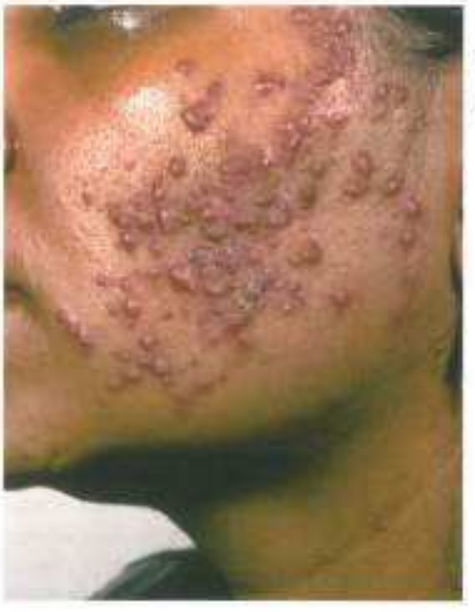


Fig. 18.122 Acneiform eruption. This severe eruption of papules and pustules on the face was caused by isoniazid.

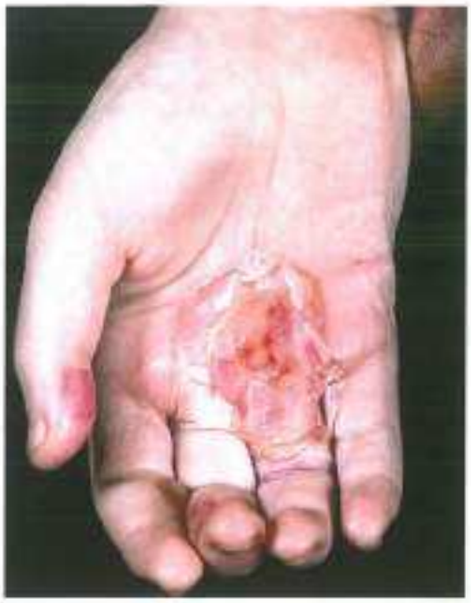


Fig. 18.123 Bullous eruptions. Bullae are common in unconscious patients, particularly on pressure areas. These resulted from a clenched fist following an epileptic fit in a man taking carbamazepine. They are sometimes known as 'fitting blisters'.

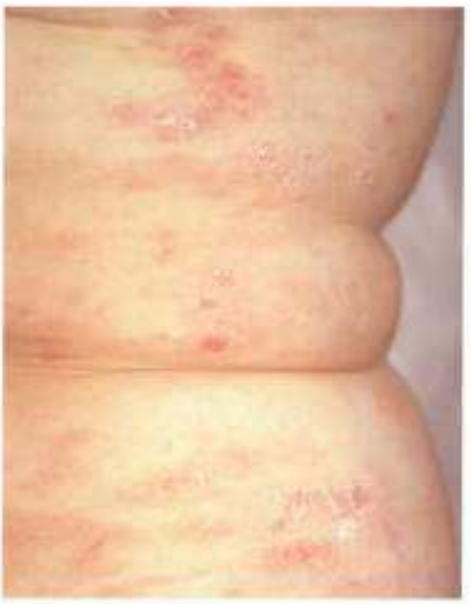


Fig. 18.124 Eczematous eruptions. The eruption, which simulated pityriasis rosea, was secondary to gold, administered for her rheumatoid arthritis.

and some endothelial cells. Xerosis, brittle curly hair, paronychia and pyogenic granulomas may also occur.

- **Psoriasiform eruptions** Practolol, a beta-blocker, produced a mucocutaneous reaction. The drug has largely been withdrawn as a result. The rash is partly psoriasiform but with features of lichen planus, eczema and lupus erythematosus. The eruption is widespread with a predilection for bony prominences. Hyperkeratosis of the palms and soles and around the fingers and toes is characteristic. Exfoliative dermatitis may result. The importance of the condition is not particularly the skin eruption, which is reversible on stopping the drug, but the involvement of mucous membranes, particularly those in association with the eye, which lead in some cases to keratoconjunctivitis sicca and scarring. Very occasionally a sclerosing peritonitis occurs. Other beta-blocking agents may produce similar psoriasiform eruptions.
- **Bullous eruptions** Individuals who have taken overdoses of barbiturates frequently develop blisters (Fig. 18.123) on areas of the skin that have been under pressure while lying immobile in an unconscious state. Bullae may occur in phototoxicity or in more severe cases of fixed drug eruptions (Fig. 18.105).
- **Eczematous eruptions** Contact dermatitis to topically applied agents is by far the most common form of eczematous drug eruption and the subject has been covered in Chapter 4. Eczematous eruptions following the ingestion of a drug are surprisingly rare. However, methyldopa may produce a discoid or seborrhoeic pattern of eczema, often with palmar and plantar involvement. These patients may have had constitutional eczema in the past. The rash responds to discontinuing the drug. Similarly, gold may produce a discoid or seborrhoeic type of eczema or even simulate pityriasis rosea (Fig. 18.124). Fatal erythroderma may result. A stomatitis may precede or accompany the eruption and eosinophilia may be present.
- **Pigmentation** Localized and generalized disturbances of pigmentation may occur. Estrogens in the contraceptive pill may produce melasma, a patchy hyperpigmentation of the forehead, cheeks, chin, bridge of the nose or upper lip. The condition is not necessarily reversible on stopping the drug. Localized hyperpigmentation can occur from the use of hydroquinones to lighten the skin or from mercury-containing cosmetics. Minocycline occasionally produces hyperpigmentation in acne cysts and scars, on the mucous (Figs 18.125 and 18.126) membranes and on

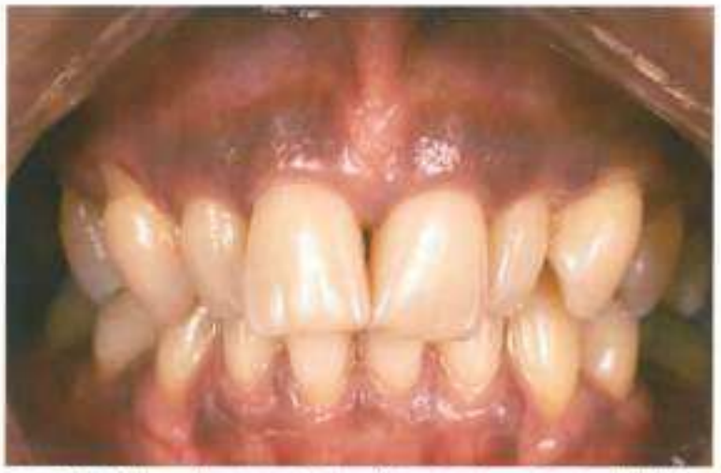


Fig. 18.125 Minocycline pigmentation. Minocycline is an effective antibiotic for acne vulgaris and rosacea. Pigmentation, however, sometimes occurs on the mucous membranes.

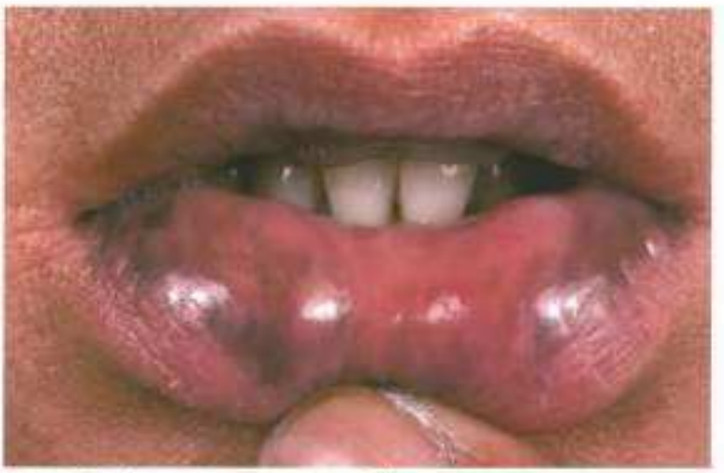


Fig. 18.126 Minocycline pigmentation. Pigmentation of the lips is a common normal variant in black skins, but may be secondary to drugs, in this case minocycline.

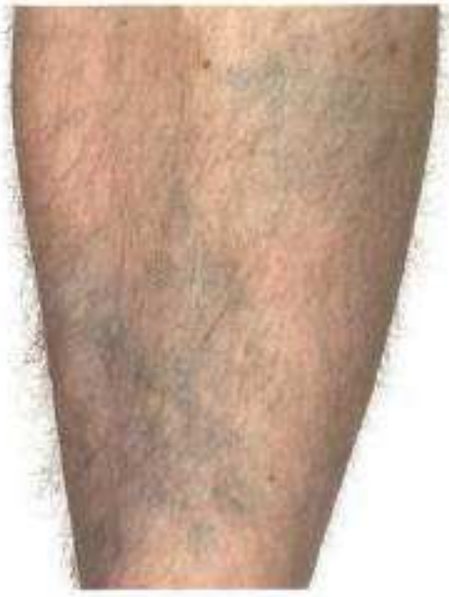


Fig. 18.127 Minocycline-induced pigmentation. A rather striking, blue discoloration may occasionally occur in patients taking minocycline. The shins are particularly affected.

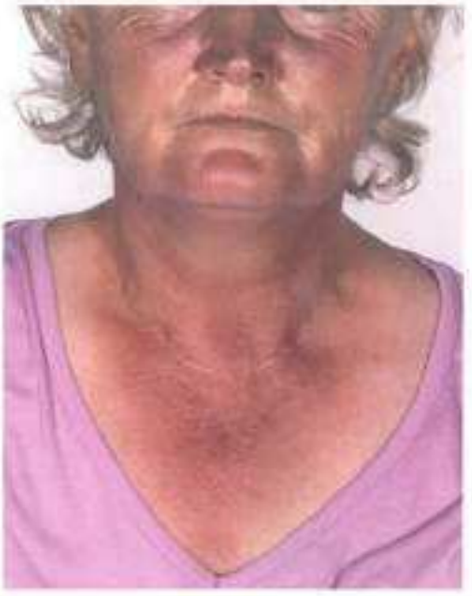


Fig. 18.128 Chlorpromazine pigmentation. A characteristic hyperpigmentation occurs on exposed areas with long-term use of chlorpromazine. It ultimately becomes generalized.

the legs (Fig. 18.127). Patients who have to take phenothiazines in high dosage on a long-term basis may develop generalized hyperpigmentation, especially with chlorpromazine (Fig. 18.128). Arsenic causes a generalized hyperpigmentation with tiny macules of hypopigmentation and the appearance is sometimes termed 'rain drop' pigmentation. Other heavy metals (Fig. 18.129) (silver, mercury, bismuth and gold) may cause pigmentation. The antimalarial drug mepacrine always produces a yellow discoloration of the skin and is usually seen in patients being treated with it for sarcoidosis (Ch. 22, Fig. 22.16). Amiodarone is a photosensitizer and may result in a patchy hyperpigmentation of exposed areas.

- **Drug-induced lupus erythematosus** A systemic lupus erythematosus-like disease may be precipitated by drugs, particularly the antihypertensive agent hydralazine. Renal and central nervous system involvement is unusual. Antihistone antibodies are often present whereas anti-DNA antibodies and serum complement are normal. The eruptions may be vasculitic, erythema multiforme-like or even bullous and resemble pyoderma gangrenosum. Procainamide, anticonvulsants and minocycline can produce the syndrome. Minocycline is rarely responsible considering how often it is prescribed for acne and rosacea, but autoantibody studies and liver function tests are probably indicated in patients who are likely to take the drug for a year or longer.

Pemphigus Sulfhydryl drugs such as penicillamine are the most common cause. It is used to treat Wilson's disease and, in lower doses, rheumatoid arthritis or primary biliary cirrhosis. Urticarial or morbilliform rashes are seen, but the most characteristic is a simulation of pemphigus vulgaris. The eruption may start as a stomatitis with flaccid blisters or erosions that bleed, are painful and show little tendency to heal. Similar erosions occur on the body. The vegetative form of pemphigus is also often seen. The histology is identical to that of pemphigus. The immuno-fluorescence may or may not be positive. The eruption clears on stopping the drug but it may take many months. Captopril may produce a similar eruption. Penicillamine also produces a characteristic atrophy of the skin (Fig. 18.130) with wrinkling,

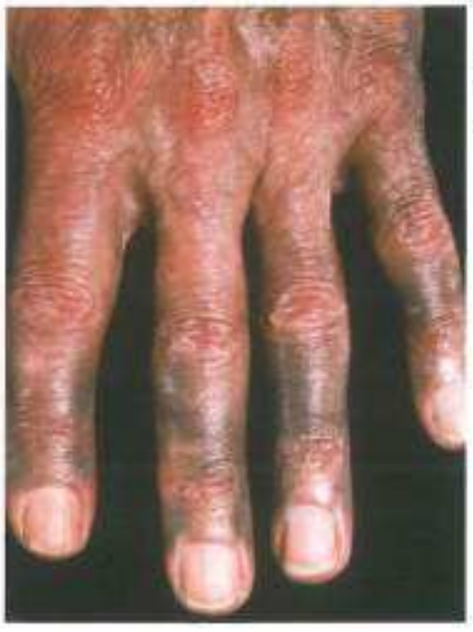


Fig. 18.129 Argyria. Heavy metals such as silver produce a remarkable pigmentation of the skin. (Courtesy of Dr Natasha Kapur.)

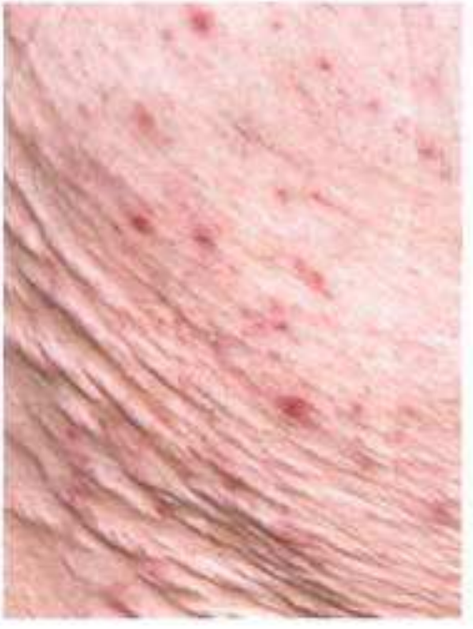


Fig. 18.130 Penicillamine-induced atrophy. High doses of penicillamine used to treat Wilson's disease may induce atrophy, purpura and wrinkling of the skin.

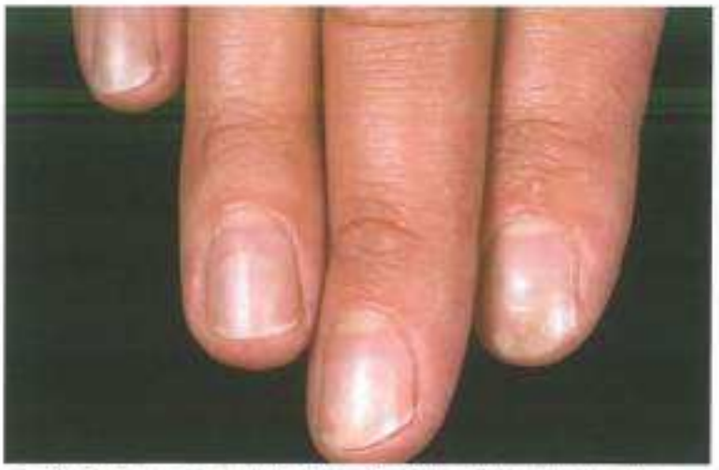


Fig. 18.131 Photo-onycholysis. Separation of the distal nail plate from the nailbed may occur as a result of a phototoxic eruption.

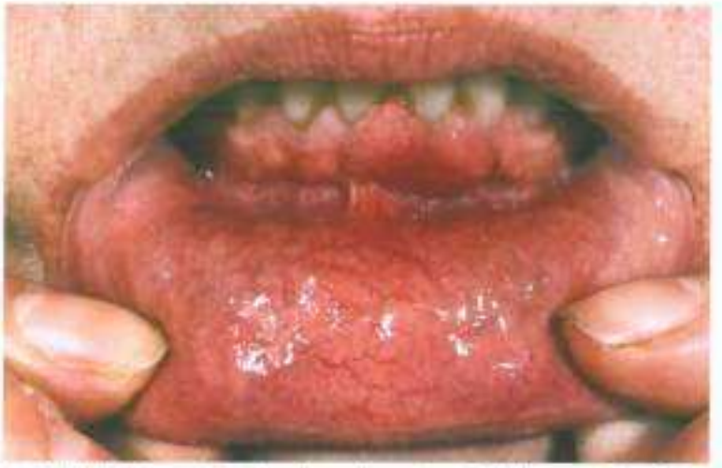


Fig. 18.132 Ciclosporin-induced gum hypertrophy. This is hypertrophy of the gums around the lower teeth. She was taking ciclosporin orally to control her pemphigus vulgaris.

purpura and blistering in pressure areas when used to treat Wilson's disease. It is lathyrogenic and alters the aldehyde cross-links required to form insoluble collagen fibres from soluble precursors. Rifampicin may precipitate pemphigus by impairing suppressive T cells resulting in proliferation of forbidden B cell clones and therefore antibodies. It behaves like pemphigus despite discontinuing the drug.

- **Pemphigoid** Frusemide and spironolactone may trigger an immunofluorescent-positive bullous pemphigoid, which resolves on stopping the drug. It occurs in younger patients, which may suggest the diagnosis.
- **Hair changes** Loss of hair (*telogen effluvium*) is a sequel of any severe illness but also may follow a drug reaction. Cytostatic agents, however, are a common cause of acute hair loss (*anagen effluvium*). There is an abrupt cessation of mitosis in the rapidly developing hair matrix cells, which either stops hair growth completely or produces a narrow defective hair shaft that fractures. It occurs after about a week of chemotherapy and is prominent after 1 or 2 months. About 10% of the hair may remain (i.e. that hair that is in a resting phase at the time of the chemotherapy) but eventually all the hair falls out after repeated treatments. The most commonly responsible drugs are cyclophosphamide, dactinomycin, daunorubicin, etoposide and vincristine. The hair usually recovers but it may have a different texture or colour. Measures to prevent it such as using a tourniquet to the scalp or hypothermia have a very limited effect. Anticoagulants also produce a diffuse alopecia, beginning after a couple of months and lasting for about 6 months. Similarly, drugs used in the treatment of hyperthyroidism may produce hair loss, either by inducing hypothyroidism or by unknown mechanisms of their own.
- **Nail changes** The most common change in the nails seen following drug administration is onycholysis. This separation of the distal part of the nail plate from the nailbed occurs particularly with the tetracyclines in association with exposure to strong sunlight (Fig. 18.131). A similar change was common with the now discontinued non-steroidal anti-inflammatory drug benoxaprofen. Beau's lines and shedding of the nails may occur after any severe drug reaction and may be seen after chemotherapy (Ch. 25, Fig. 25.67).
- **Stomatitis** A sore tongue and oral ulceration may occur with any drug reaction but is often seen with gold toxicity or during chemotherapy with the antimetabolites (e.g. 5-fluorouracil and methotrexate) and the antitumour antibiotics (e.g. bleomycin or daunorubicin). The oral mucosa has a high mitotic index and is, therefore, vulnerable; the changes are usually seen within the first week. There is erythema and oedema and subsequently ulcers, which are focal at first, and xerostomia. This is an effect of direct toxicity but it may occur indirectly from effects on the bone marrow, particularly with granulocytopenia. It is usually seen after 2 weeks when the therapeutic nadir of chemotherapy is reached. Bacteria, fungi (particularly *Candida* sp.) and viruses (such as herpes simplex and zoster) may also cause stomatitis during chemotherapy. Ciclosporin produces gum hypertrophy (Fig. 18.132).
- **Anal ulceration** Nicorandil may cause this and sometimes perivulvar, perioral and peristomal ulceration.
- **Erythroderma** Erythroderma and toxic epidermal necrolysis are the most severe forms of drug reaction. Any drug may be responsible but notable causes are allopurinol, gold, penicillamine, sulphonamides, isoniazid and ampicillin.
- **Drug reaction with eosinophilia and systemic symptoms (DRESS)** Also known as the *drug hypersensitivity syndrome*, this is a condition of high fever, facial oedema (Fig. 18.133), an ichthyotic erythroderma (Figs

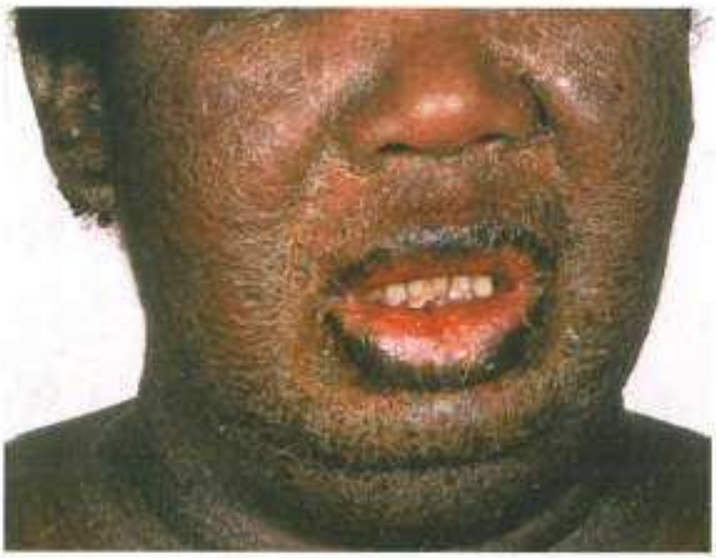


Fig. 18.133 DRESS. The facial involvement is often pronounced with follicular pustulation, oedema and desquamation. It is particularly common in black skins.

Fig. 18.134 DRESS. The rash begins as a maculopapular toxic erythema, but becomes quite dry, ichthyotic and erythrodermic. There may be a fever, leucocytosis, eosinophilia, lymphadenopathy and deranged liver function. Anticonvulsants are usually responsible.

Fig. 18.135 DRESS. The eruption becomes extensive and the patient is unwell with fever, hepatitis and lymphadenopathy. Liver and multiorgan failure may ensue.

18.134 and 18.135), lymphadenopathy, eosinophilia, elevated CRP and deranged liver function tests occurring 3–6 weeks after the ingestion of a drug. These are often anticonvulsants (phenytoin, carbamazepine, phenobarbitone, lamotrigine and valproate), sulphonamides, minocycline or allopurinol. Lymph node biopsy may show hyperplasia, pseudolymphoma or indeed may progress to frank lymphoma. The hepatitis may be severe and multiorgan failure may occur and be fatal. It is most common in black skins and may be associated with viral infections including HIV (abacavir is particularly associated with this), HHV6 and 7. It requires withdrawal of the drug, pulse methylprednisolone and sometimes IVIG.

- **Acute generalized exanthematous pustulosis (AGEP)** This is an acute febrile drug eruption (also known as *toxic pustuloderma*), characterized by small non-follicular pustules on a background of erythema and oedema, which is often confused with generalized pustular psoriasis. It particularly affects the face and intertriginous areas, but may involve the trunk and limbs. There is a very short interval of a day or so between exposure to the drug and the reaction, which suggests immunological recall and prior sensitization. Marked leucocytosis (with neutrophilia), some eosinophilia but normal liver function tests are present. The histology shows massive oedema in the superficial dermis, exocytosis of eosinophils, spongiform pustules and necrosis of keratinocytes. The common responsible drugs are β-lactams, macrolides, vancomycin, doxocycline, and calcium channel blockers, especially diltiazem.
- **Palmar plantar erythrodysaesthesia syndrome** This is particularly seen during chemotherapy with cytarabine, doxorubicin, 5-fluorouracil, liposomal anthracyclines and capacitabine. There is a prodrome of dysaesthesia of palms and soles with burning tenderness and subsequently symmetrical, well-demarcated, oedematous, erythematous plaques (Fig. 18.136), particularly over the lateral sites of the fingers and the thenar and hypothenar eminences. It is very painful and limits activity. It is postulated that the drug is concentrated in and secreted by the sweat

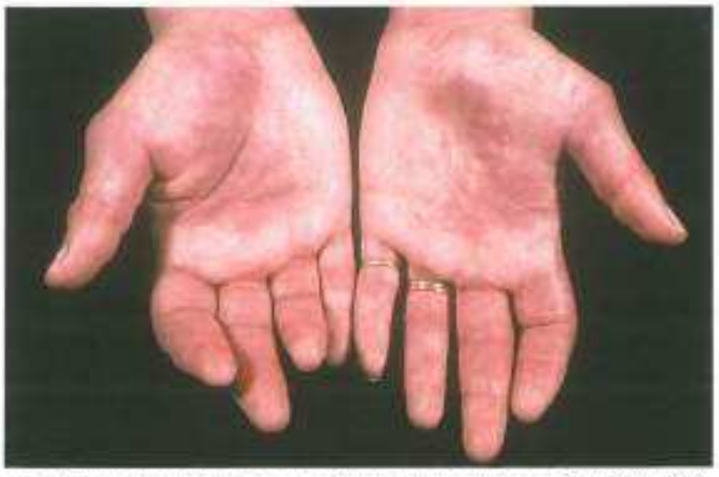


Fig. 18.136 Palmar plantar erythrodysaesthesia syndrome. There is burning of the skin followed by a well-demarcated erythema. Chemotherapeutic agents, e.g. cytarabine, doxorubicin and 5-fluorouracil are the common causes.

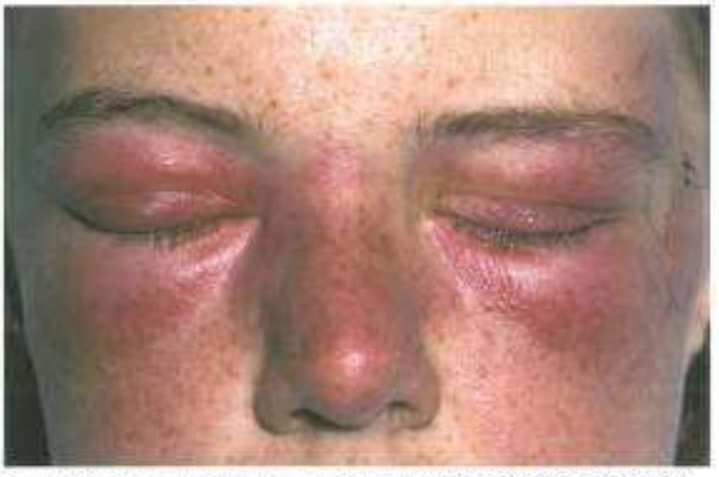


Fig. 18.137 Neutrophil eccrine hidradenitis. A unilateral or bilateral periorbital erythematous oedema may occur during treatment of acute myeloid leukaemia.

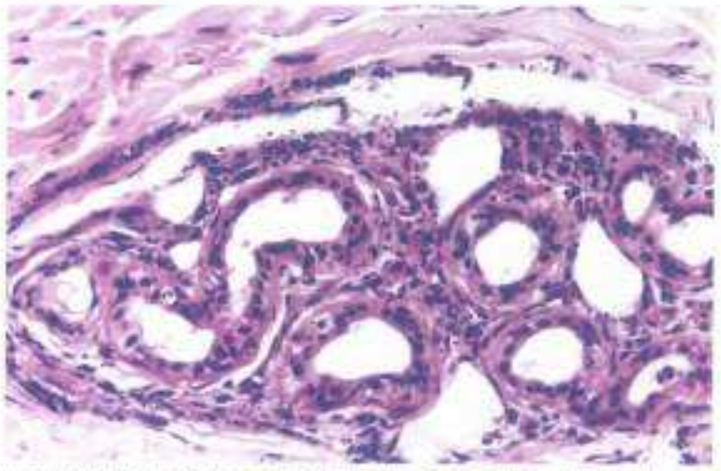


Fig. 18.138 Neutrophil eccrine hidradenitis. There is a heavy infiltrate of neutrophils around the eccrine sweat coils, with necrosis of the epithelial cells lining them or their ducts.

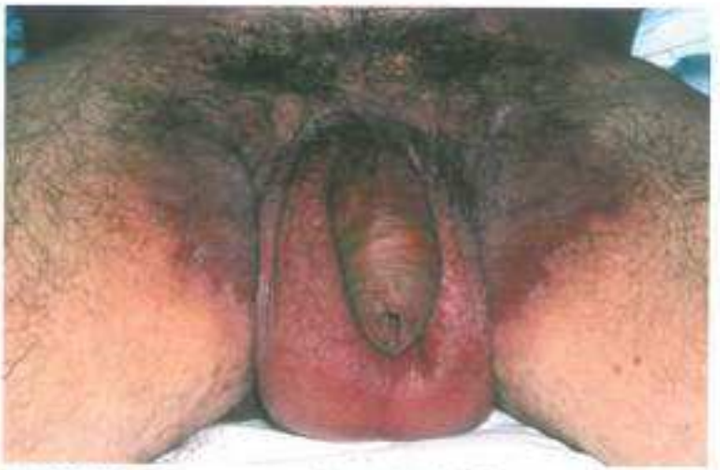


Fig. 18.139 Eccrine squamous syringometaplasia. This may occur during high-dose chemotherapy, particularly with cytarabine. Red oedematous plaques may become erosive and painful in the groin or axilla.

glands and there is a direct toxic damage. Hence the palms and soles are affected. Pyridoxine 150 mg twice daily has been reported as being helpful but sometimes the drug has to be stopped.

- **Neutrophil eccrine hidradenitis** A unilateral or bilateral, periorbital, erythematous, oedematous eruption (Fig. 18.137) has been described in patients with acute myeloid leukaemia in association with cytarabine, anthracyclines or mitoxantrone. Histologically there is an impressive infiltrate of neutrophils around eccrine coils and necrosis of the epithelial cells lining the coils or the ducts (Fig. 18.138), despite its occurrence during the granulocytopenia induced by the chemotherapy. Sweet-like lesions may also occur.
- **Eccrine squamous syringometaplasia** This is another condition involving the sweat glands. It is a distinctive, clinical condition of red, oedematous plaques or confluent erythema, which may become erosive and painful in the intertriginous areas particularly of the axillae and groins (Fig. 18.139); there may also be palmar and plantar erythema and oedema. There is metaplasia of the cuboidal epithelial cells of the eccrine sweat glands histologically. It is seen during or after pretransplantation conditioning regimens with high-dose chemotherapy.
- **Methadone and heroin** 'Mainlining' results in infection, necrosis and scarring of the skin (Fig. 18.140).

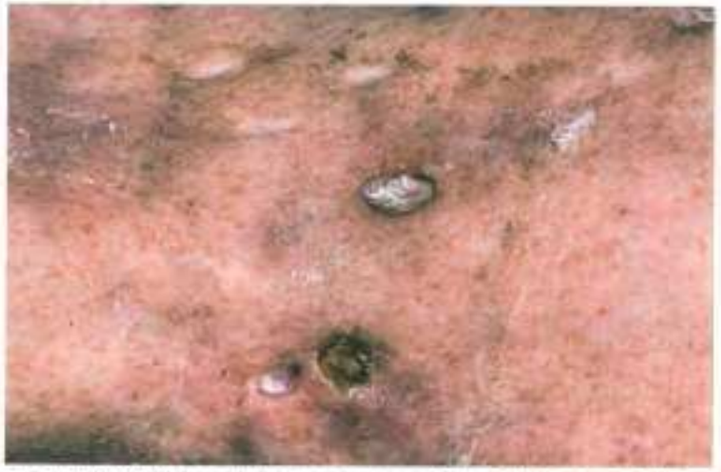


Fig. 18.140 Methadone-induced scarring and fibrosis. Intravenous injection of narcotics may cause sepsis, necrosis, scarring and fibrosis of the skin.

Light eruptions

Terrestrial sunlight extends from 290 to 400 nm. The range 290–320 nm is known as ultraviolet B (UVB) and 320–400 nm as ultraviolet A (UVA or longwave ultraviolet light). UVB is principally responsible for sunburn and its effects on the ageing process and cutaneous neoplasia have been covered in Chapter 10. On the whole, UVA does not produce burning of the skin, which is why 'sunbeds' (which deliver UVA) are a popular means of acquiring a suntan. It penetrates deeper in the dermis than UVB and has a major effect in ageing the skin. It temporarily inhibits the function of Langerhans' cells, which are responsible for immune surveillance of the skin and may, therefore, play a significant role in causing skin cancer. UVA passes through window glass whereas UVB is absorbed by the glass and does not. Common photodermatoses include:

- Immunological – polymorphic light eruption, juvenile spring eruption, Hutchinson's actinic prurigo, solar urticaria and chronic actinic dermatitis
- Metabolic – porphyria, pellagra
- Genodermatoses – xanthoma pigmentosum, Cockayne, Kindler syndrome, IBID
- Chromosomal instability – Bloom's syndrome, Rothmund–Thomson syndrome
- Drug-induced phototoxicity and photoallergy
- Photoageing
- Photoaggravated dermatoses – several, including lupus erythematosus, Darier's disease and herpes simplex.

Phototoxic drug eruptions, the polymorphic light eruption and chronic actinic dermatosis are discussed here. The rest are discussed elsewhere.

PHOTOTOXIC DRUG ERUPTIONS

An erythema of light-exposed areas of the skin and sometimes the fingernails, secondary to the ingestion of a photosensitizing drug.

Aetiology

Certain drugs regularly produce a phototoxic eruption. Some are always phototoxic, for example psoralens, but in others the effect is idiosyncratic. The mechanism is not completely understood, although in some it is a true delayed hypersensitivity reaction (e.g. factory workers who manufacture chlorpromazine may become sensitized and then develop phototoxicity), but most require intense ultraviolet exposure for a phototoxic drug eruption to manifest itself.

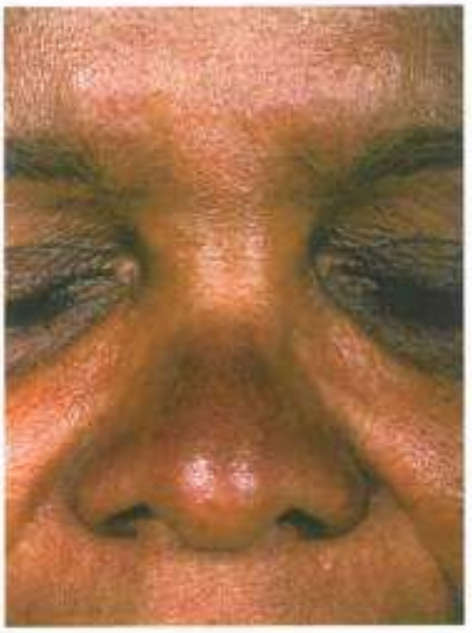


Fig. 18.141 Drug-induced photosensitivity. The erythema is less apparent in black skin, but the involvement of the nose and upper chest (Fig. 18.142) in this patient suggested phototoxicity, in this case caused by a thiazide.

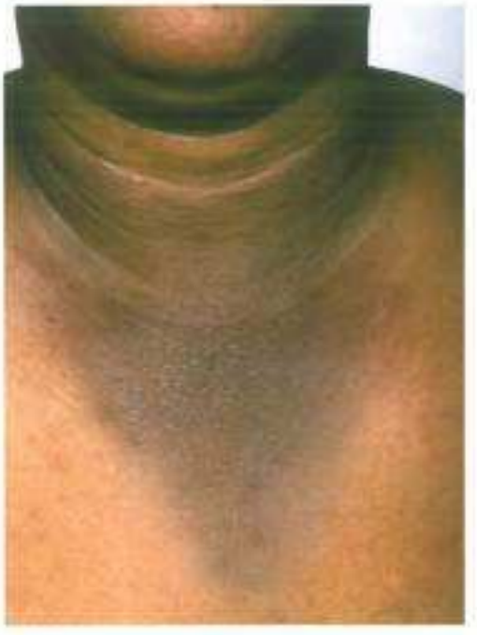


Fig. 18.142 Drug-induced photosensitivity. Not only the nose was involved (Fig. 18.141) but also the 'V' below the neck which was highly suggestive of phototoxicity.

Common photosensitizing drugs are:

- Phenothiazines, especially chlorpromazine and promethazine
- Tetracyclines, especially demethylchlortetracycline, doxycycline and vibramycin
- Sulphonamides
- Diuretics, especially thiazides and nalidixic acid
- Non-steroidal anti-inflammatory drugs, especially piroxicam and naproxen
- Chlorpropamide
- Amiodarone
- Psoralens (systemic and topical)
- Antifungals, especially voriconazole and posoconazole.

Clinical Features

Symptoms

There is an itchy rash.

Morphology

The eruption may be lichenoid, occasionally erzematous or, more likely, an exaggerated sunburn, which may be followed by blistering.

Distribution

The face (Fig. 18.141), 'V' below the neck (Figs 18.142 and 18.143) and backs of the hands (Fig. 18.144) are especially involved, but any exposed areas can be affected. Characteristically on the face, the areas under the nose, upper eyebrows and chin and behind the ears will be relatively spared, because these areas are shaded.

Management

Management involves stopping the drug, applying topical steroids and, if severe, 30 mg of prednisolone daily reduced by 5 mg every fourth day. The patient and doctor should record the occurrence.

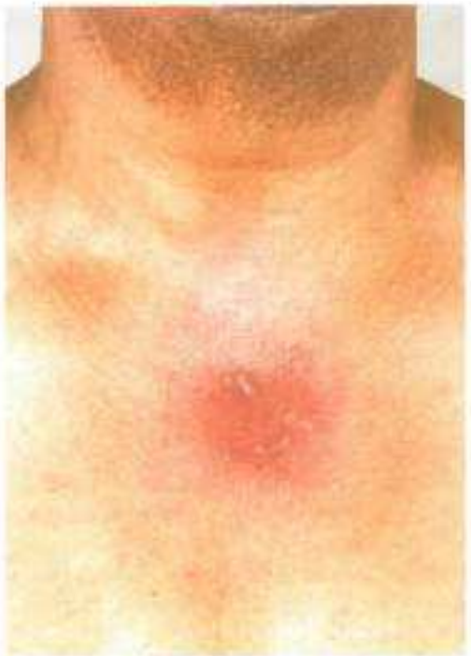


Fig. 18.143 Drug-induced photosensitivity. There is erythema and oedema on the exposed sites, the 'V' of the upper chest. This distribution would suggest the diagnosis.

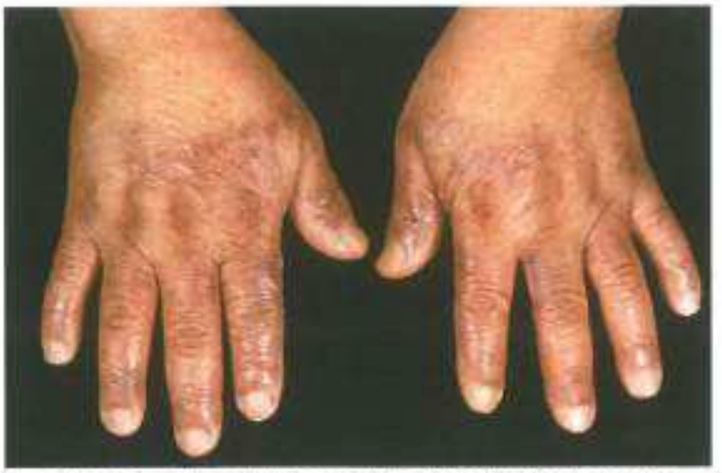


Fig. 18.144 Drug-induced photosensitivity. The backs of the hands are the classic sites to be involved in light-induced eruption. This is the same patient as in Fig. 18.143.

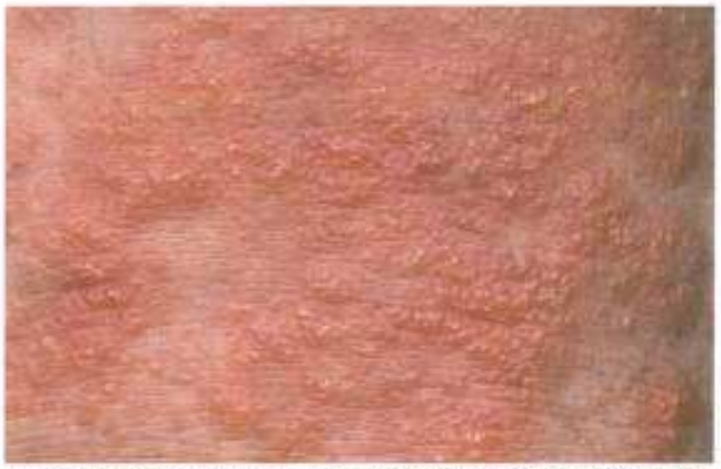


Fig. 18.145 Polymorphic light eruption. Very itchy, red, oedematous papules, which may coalesce into plaques; occur 1 or 2 days after exposure to light.

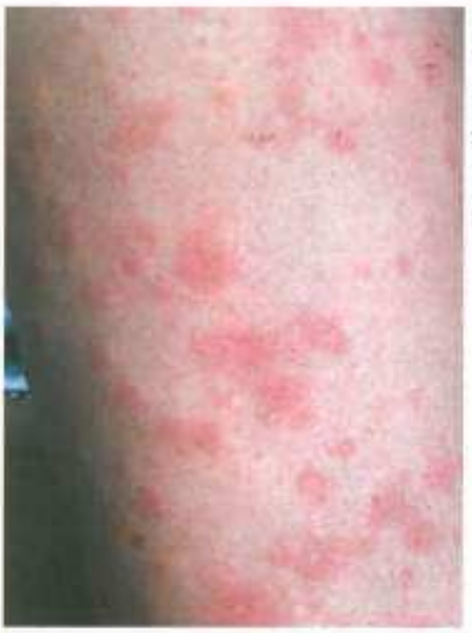


Fig. 18.146 Polymorphic light eruption. Exposed areas such as the backs of the hands and forearms are affected. Ultraviolet A is mainly responsible and may penetrate window glass.

POLYMORPHIC LIGHT ERUPTION

A common hypersensitivity to ultraviolet light that results in a pruritic eruption on exposed areas, although usually sparing the face.

Aetiology

This is common in Caucasians although it can occur in pigmented races. It usually commences in young adults (occasionally in childhood) and occurs particularly in the spring or early summer. Skin that is pale after the winter is more vulnerable than that which is already tanned, although this is not true of all patients. Most patients are sensitive to UVA, some to UVB and a few to both. Although it may occur in the UK, it is more frequent when the patient travels to a sunny climate.

Clinical Features

Symptoms

An itchy rash (prickly heat) occurs 24–48 hours after the first sun exposure.

Morphology

Red, itchy, oedematous papules (Fig. 18.145) occur that may coalesce into plaques.

Distribution

Exposed parts, in particular the backs of the hands, forearms, legs (Fig. 18.146) and dorsum of the feet. It may be more extensive. The face is usually spared, perhaps because it is continually exposed to ultraviolet and the skin is, therefore, in some way 'hardened'.

Variants of light eruption are:

- **Hutchinson's summer prurigo** excoriated papules occur not only on exposed but also on covered areas (Fig. 18.147) and sometimes persist through the winter months. It usually commences in childhood, unlike the polymorphic light eruption, and may or may not clear in adult life.
- **Hydroa vacciniforme**. It consists of umbilicated vesicles (Fig. 18.148) that heal leaving varioliform scars which occurs on exposed areas in children. It is an extremely rare and as yet unclassified, light eruption.

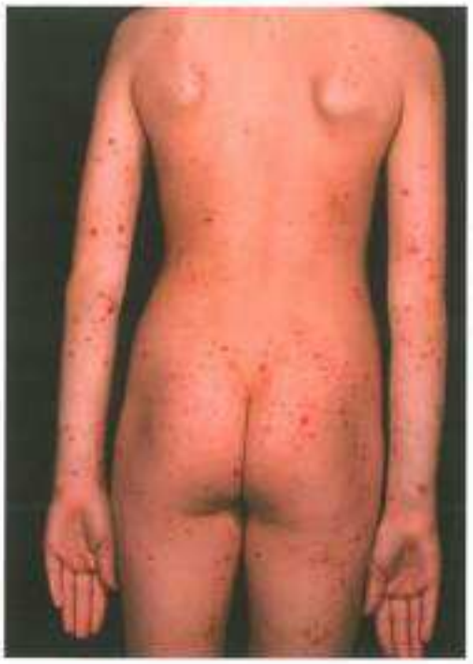


Fig. 18.147 Hutchinson's summer prurigo. Excoriated papules occur on both exposed and covered parts. It starts in childhood and may persist into adult life. It responds, however, to thalidomide. (With permission from Bolognia JL, Jorizzo JL, Rapini RP, et al: Dermatology, 2nd edition. London: Elsevier, 2008.)

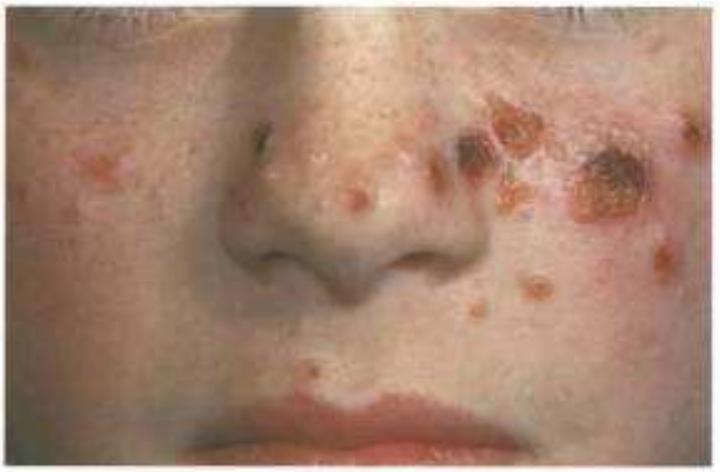


Fig. 18.148 **Hydroa vacciniforme.** Umbilicated vesicles occur on exposed areas in childhood and leave varioliform scars. Epstein–Barr virus (EBV) has been detected in dermal infiltrates.

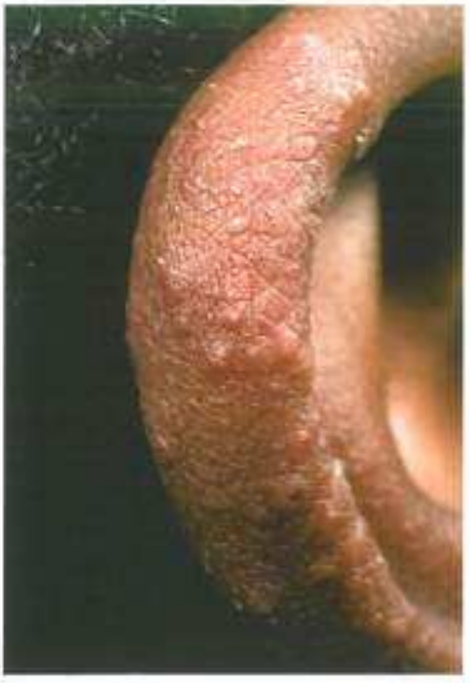


Fig. 18.149 Juvenile spring eruption. The ears are affected with papulo-vesicles for about a week in the spring. There may be cervical adenitis.

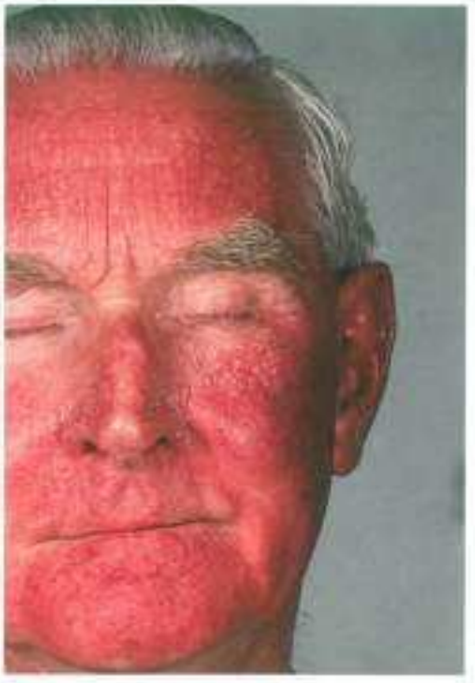


Fig. 18.150 Chronic actinic dermatitis. The light-exposed areas are affected. Note the sparing of the eyelids. It is a chronic disorder, but does respond to azathioprine.

The histology shows epidermal necrosis with a dense dermal lymphocytic infiltrate. Severe disease is occasionally associated with EBV-driven haematological disorders.

- **Juvenile spring eruption** a disorder of boys, which affects the ears in a papulo-vesicular manner (Fig. 18.149). It heals quickly but may recur the next spring. The pathology is that of PMLE.

Management

The patient invariably connects the eruption with the sun so the diagnosis presents little problem, but lupus erythematosus needs to be considered if the condition persists. It usually lasts for about a week even if sun exposure continues and then resolves without scarring. It recurs most years but eventually remits. The polymorphic light eruption may be reproduced with a solar simulator (an expensive piece of equipment available in relatively few centres). It is the only way, however, that the wavelength responsible in any one individual can be detected.

The immediate management is oral antihistamines, topical calamine, potent topical steroids (although they only have a limited effect) and, if severe, systemic steroids (commencing at 30 mg prednisolone daily, and reduced over the ensuing 10 days) are effective.

After such an eruption has occurred, many patients will consult the practitioner for advice on how to prevent a recurrence. It is clearly unwise to sunbathe, but the condition can occur with ordinary exposure such as walking in the sun. Therefore, long-sleeved shirts and trousers are advisable, although it is difficult for some patients to accept this, especially as the light eruption will occur through thin material. Broad-spectrum sunscreens are worth trying but, since UVA is often responsible, these are not always satisfactory because the majority of sunscreens do not block out UVA very efficiently. Opaque sunscreens containing titanium dioxide or zinc oxide are effective but may be unacceptable. Microfine titanium dioxide is an alternative.

More toxic measures to prevent distressing symptoms include:

- **Systemic steroids** Prednisolone, 20 mg daily starting 2 days before the holiday and taken throughout, is effective, but recurrent courses should be used with caution.
- **Chloroquine and hydroxychloroquine** The eruption may be prevented by chloroquine, 200 mg daily. Since it causes various forms of reversible keratitis, and even an irreversible retinopathy, hydroxychloroquine (plaquenil) is preferable.
- **Ultraviolet light** A course of narrowband UVB prior to a holiday may accustom the skin to ultraviolet and produce a protective tan, although a polymorphic light eruption may actually occur during this therapy. Equally a course of photochemotherapy (PUVA) may be tried. This is often highly effective, though a polymorphic light eruption may occur during it. Since skin cancer results from cumulative solar exposure, this treatment should be prescribed judiciously as the effects of the ultraviolet irradiation are irreversible.

CHRONIC ACTINIC DERMATITIS

A chronic photosensitivity to visible or ultraviolet light that particularly affects elderly males.

Aetiology

Originally, *actinic reticuloid* was the name given to a condition that affected exclusively males who had extreme photosensitivity necessitating a nocturnal existence, and a malignant 'reticuloid' histology. The spectrum of the condition has now widened and it has been renamed chronic actinic dermatitis.

Patients frequently have positive patch and photopatch tests to a number of allergens, but allergen avoidance may not effect much improvement. The condition may be caused by chronic antigenic stimulation. Light testing indicates a photosensitivity ranging throughout the UVB and the UVA ranges.

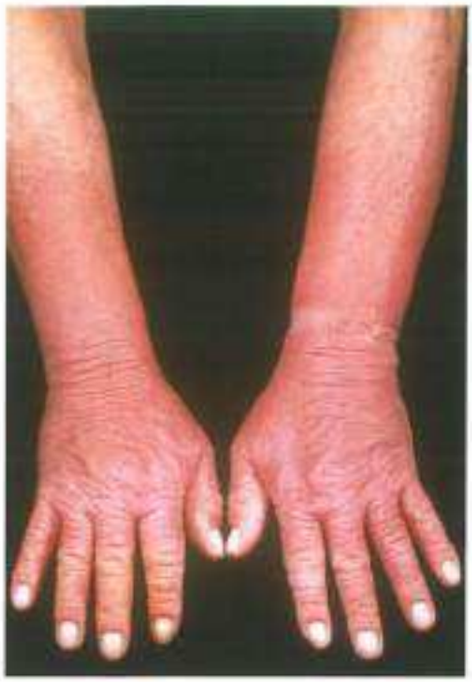


Fig. 18.151 Chronic actinic dermatitis. The involvement of the back of the hand, and forearms are very suggestive of a phototoxic process. Note the sparing from the watch strap.

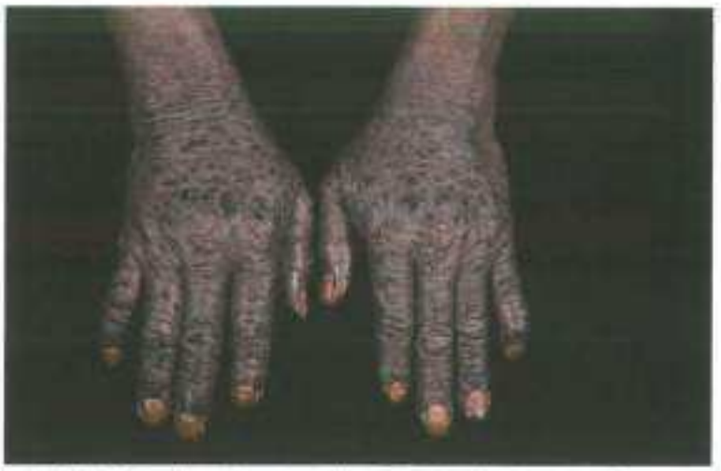


Fig. 18.152 Chronic actinic dermatitis. The backs of the hands and fingers are involved. Note the sharp cut-off at the wrists where the forearms would be protected by a long-sleeved shirt.

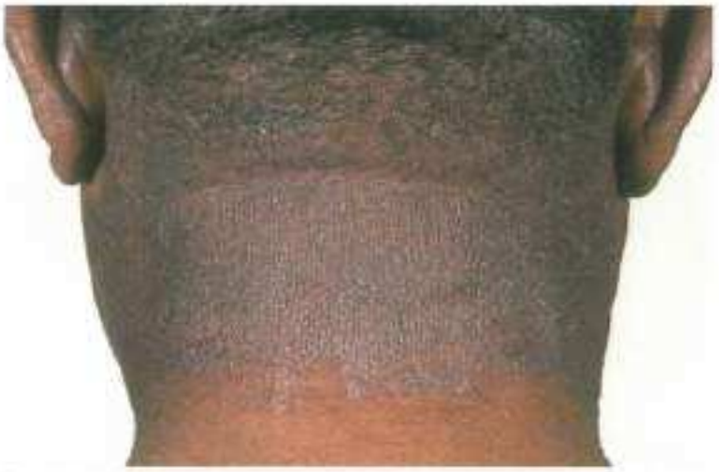


Fig. 18.153 Chronic actinic dermatitis. The eczematous changes of light-exposed skin are contrasted with the lower neck, which would have been protected by his shirt.

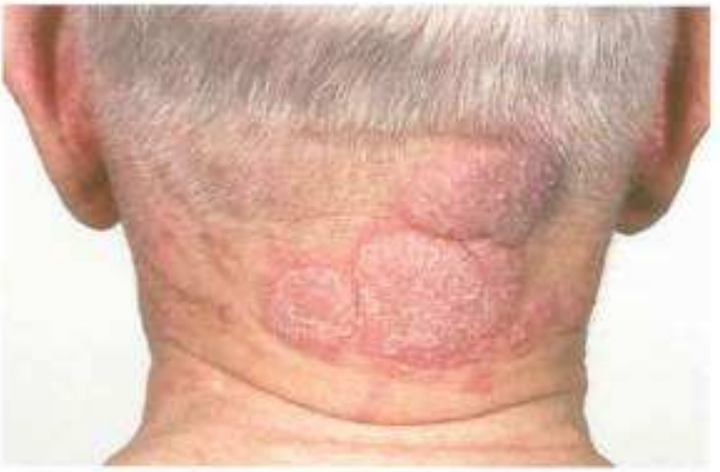


Fig. 18.154 Chronic actinic dermatitis. With time, the skin becomes infiltrated simulating a lymphoma, hence its original name of actinic reticuloid.

Clinical Features

Symptoms

An insidious seasonal rash, often misdiagnosed as eczema, on the face and hands.

Morphology

The skin is red, scaling and thickened, and ultimately thrown into folds producing a leonine appearance.

Distribution

The face (with sparing of the eyelids, behind the ears and under the chin) (Fig. 18.150), sides of the neck, 'V' of the front of the neck, forearms (Fig. 18.151) and hands (Fig. 18.152). A sharp cut-off between light-exposed and covered skin is very suggestive of phototoxicity (Figs 18.153 and 18.154). It may gradually spread to covered sites.

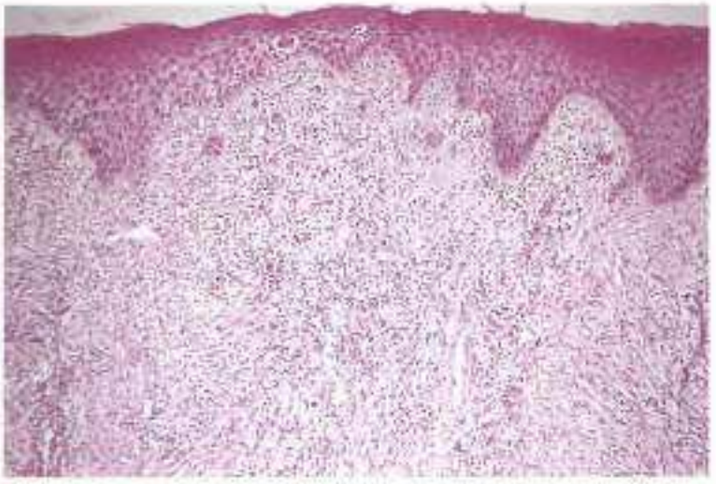


Fig. 18.155 Chronic actinic dermatitis (actinic reticuloid). There is patchy hyperkeratosis, marked but irregular acanthosis and two small intraepidermal collections of lymphoid cells that resemble the Pautrier microabscesses of mycosis fungoides.

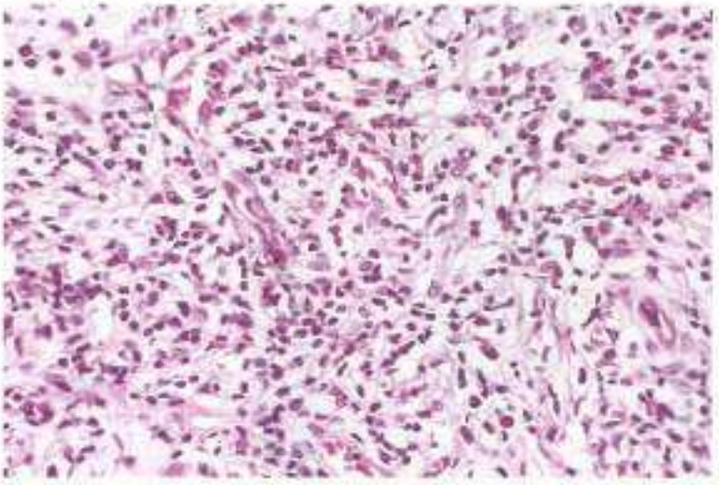


Fig. 18.156 Chronic actinic dermatitis. There is a fairly dense, chronic, inflammatory cell infiltrate that occupies the dermis and consists of lymphocytes, plasma cells, eosinophils and histiocytes. Some of the lymphocytic nuclei are irregular and hyperchromatic, simulating mycosis fungoides.

Management

The histological features vary from those of a mild, non-specific, chronic dermatitis to a histology virtually indistinguishable from that of mycosis fungoides (Figs 18.155 and 18.156). Phototesting is helpful to establish the wavelength involved. Photoprotection is essential. Azathioprine, methotrexate, ciclosporin and mycophenolate mofetil are all effective. The condition very occasionally progresses to lymphoma.

Blistering disorders of the skin 19

Blisters are a common cutaneous physical sign and usually result from banal causes such as insect bites, herpes simplex, impetigo or burns. The primary blistering disorders of the skin are uncommon. Their nature was clarified when Lever separated bullous pemphigoid from pemphigus as a distinct clinical entity in 1953. The whole subject was, however, transformed by the technique of immunofluorescence when Jordan and Beutner in 1967 demonstrated IgG at the epidermal basement membrane in bullous pemphigoid and circulating IgG antibodies directed against the basement membrane in bullous pemphigoid and against epithelial cells in pemphigus vulgaris. Van de Meer discovered IgA deposits in the dermal papillae in dermatitis herpetiformis, which established a diagnostic test for this blistering disease.

The susceptibility to these diseases is in part genetic and ethnic in that pemphigus is most common in Indians and Jews whereas pemphigoid is more likely to be seen in Anglo-Saxons. Drugs may precipitate a blistering disorder, for example penicillamine may induce pemphigus, and many of these disorders have other autoimmune associates.

The diagnosis is made partly clinically and then confirmed with immunofluorescence tests, which are more important than routine histopathology. Electron and immunoelectron microscopy and the identification of the target antigens have greatly facilitated the understanding of these disorders, and indeed many variants of pemphigus and pemphigoid have now been identified as a result of these tests.

The techniques of immunofluorescence involve the raising of antibodies to human immunoglobulin by injection into an animal. These antibodies are labelled with fluorescein, and incubated either with the patient's skin (direct immunofluorescence) or with the patient's serum and a foreign substrate, such as monkey oesophagus (indirect immunofluorescence). In the direct test, if antibody is present it will be recognized by the fluorescein-labelled antibody and deposited and can be visualized as a pale green fluorescence. In the indirect test, if antibodies are present in the serum they will be labelled with the anti-human antibody conjugated with fluorescein, deposited at the target site on the foreign substrate and will fluoresce.

Bullous pemphigoid

A serious condition characterized by itchy tense blisters caused by circulating antibodies against heterogeneous hemidesmosomal molecules.

Aetiology

It is relatively common in the elderly, affects both sexes equally and all races. It is an autoimmune process and may occur with myasthenia gravis, pernicious anaemia, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus and Hashimoto's thyroiditis. It is also more common in patients with psoriasis. Childhood bullous pemphigoid does occur. It is extremely rare, but the immunofluorescent findings are identical to those of the adult disease. It may also occur in pregnancy (Ch. 28).

Circulating IgG antibodies to the basement membrane zone of the dermo-epidermal junction may be demonstrated in the sera by indirect immunofluorescence. Direct immunofluorescence is also positive. A clear green band of fluorescence is visible as a result of the interaction of the labelled antibody with the antigenic lamina lucida of the basement membrane. Complement (C3) deposition is also present. The interaction of the autoantibodies with the target antigens in the basement membrane zone is followed by activation of complement and release of tissue-destructive enzymes by granulocytes and eosinophils. IgG and C3 are also found in a linear pattern at the basement membrane on direct immunofluorescence in epidermolysis bullosa acquisita, mucous membrane pemphigoid, pemphigoid gestationis and bullous systemic lupus erythematosus. Using the technique of salt (sodium chloride)-split skin immunofluorescence, it can be shown that the antibodies in bullous pemphigoid and pemphigoid gestationis deposit on the epidermal side of the split whereas those in epidermolysis bullosa acquisita and bullous systemic lupus erythematosus deposit on the dermal side. In most cases of mucous membrane pemphigoid, the antibodies attach to the epidermal side, but the antilaminin 5 variant has IgG antibodies binding to the dermal side. This is important diagnostically and therefore therapeutically, because for example, epidermolysis bullosa acquisita, unlike bullous pemphigoid, may not respond to systemic steroids.

The immunoglobulins can be shown by immunoelectron microscopy to be localized to the hemidesmosomes. Immunoprecipitation techniques have shown them to be directed against the bullous pemphigoid antigen BPAG 1 (230 kDa) or BPAG2 (180 kDa). Patients with antibodies against BPAG2 have a worse prognosis and a risk of death within 1 year.

Several clinically distinct variants share immunopathological features with bullous pemphigoid. These include *pemphigoid nodularis* (features of prurigo nodularis and bullous pemphigoid), *dyshidrosiform pemphigoid* (dyshidrotic eczema overlapping with bullous pemphigoid), *pemphigoid vegetans* (where vegetating lesions may be interspersed with the blisters) and *erythrodermic bullous pemphigoid* (in which erythroderma may occur in the presence or absence of blisters but immunofluorescence is positive). A bullous pemphigoid phenotype has been described in the Japanese, who have 200 kDa^+ antibodies, which react to the dermal side of split skin, but not to conventional bullous pemphigoid antigens.

BPAG1 was the first to be characterized and is intracellular and localized to the dense plaque of the hemidesmosome. The gene for BPAG1 has been cloned and is on the short arm of chromosome 6. The gene for BPAG2 is on the long arm of chromosome 10. BPAG2 is in the hemidesmosome but the antibodies react with the extracellular portion, which interconnects with the anchoring filaments. Pemphigoid gestationis has the same binding site as BPAG2.

There is controversy over whether bullous pemphigoid may be associated with malignant disease, particularly as it may be argued that malignant disease is more common in the elderly anyway. It should be looked for, however, in patients with oral ulceration (which is unusual in bullous pemphigoid) and in seronegative patients.

Clinical Features

Symptoms

Intensely itchy blisters.

Morphology

These blisters are full of clear fluid initially, are tense (Fig. 19.1) and are quite firm to feel. They start as tiny vesicles but rapidly enlarge and coalesce to form many bullae. They are usually (Fig. 19.2), but not always (Fig. 19.3), surrounded by erythema. The blisters eventually become haemorrhagic and break, leaving behind denuded, eroded skin, often covered with scabs. The lesions may become secondarily infected, and the clear blister fluid becomes purulent and yellow crusts form. Although the blisters may be quite large (Fig. 19.4), they heal without scarring, although milia may be apparent (Fig. 19.5). Occasionally, in the early stages of the disease, the lesions are of a more urticarial nature (Fig. 19.6) but are much more persistent than ordinary urticaria. Ultimately frank blisters appear.

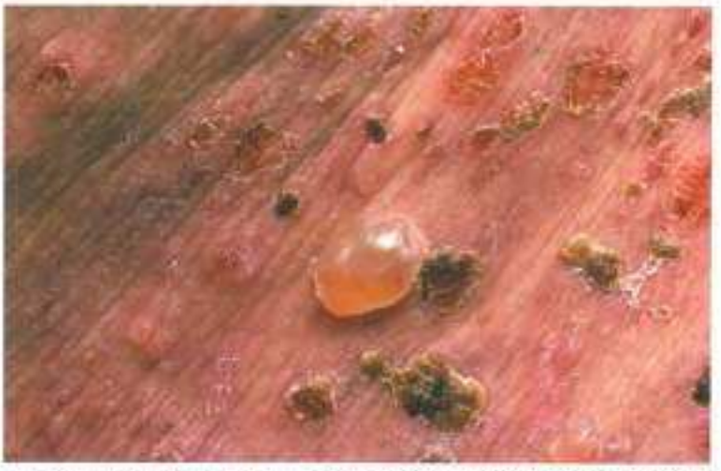


Fig. 19.1 Bullous pemphigoid. Large tense blisters are characteristic, in contrast to the flaccid blisters of pemphigus, where the split is within the epidermis.

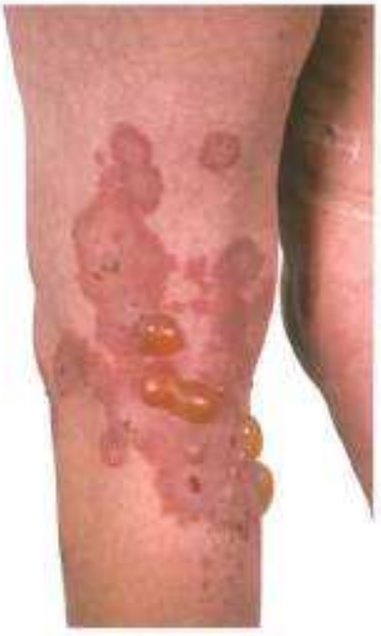


Fig. 19.2 Bullous pemphigoid. The blisters may be surrounded by erythema. They often commence on the thighs, and are intensely pruritic.

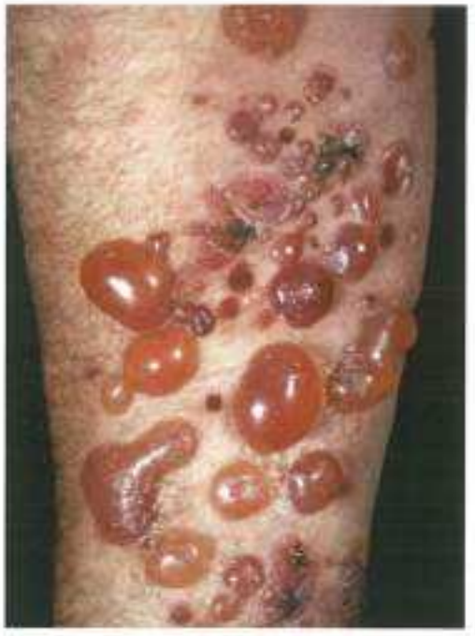


Fig. 19.3 Bullous pemphigoid. Eventually many blisters are present at various stages of development. They are not always surrounded by erythema.

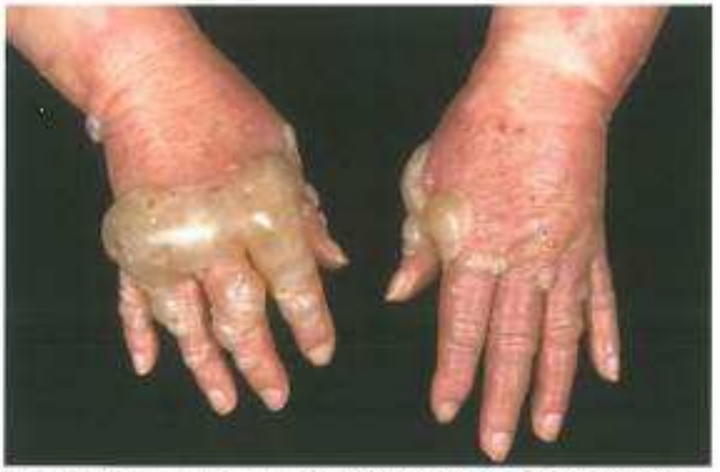


Fig. 19.4 Bullous pemphigoid. This elderly lady had widespread itchy blisters, which were particularly striking on the backs of her hand.

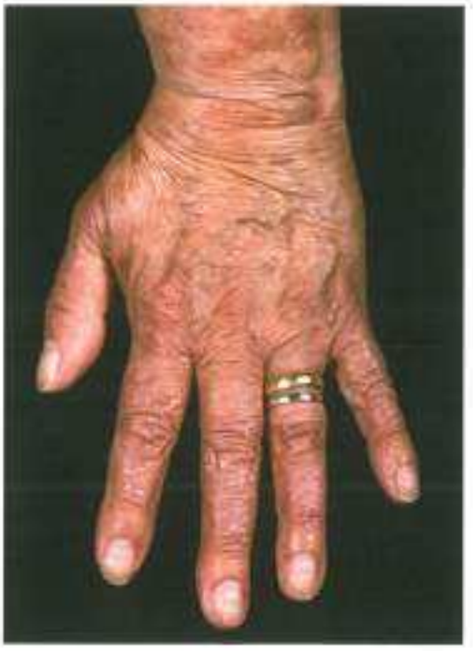


Fig. 19.5 Bullous pemphigoid. She (Fig. 19.4) was treated successfully with prednisolone and azathioprine. She subsequently remained in remission without treatment. Note the milia, which may result from any blistering process that involves the basement membrane. Beau's lines of the nails are present secondary to temporary disturbance of nail growth due to the systemic toxicity of the illness.

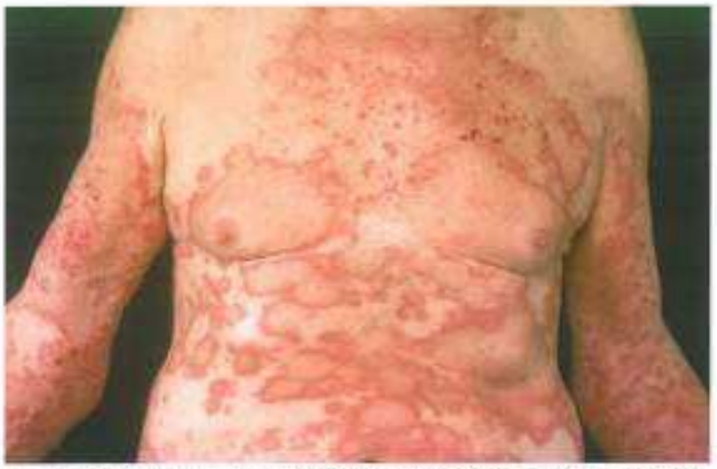


Fig. 19.6 Bullous pemphigoid. An itchy figurate erythema or urticated eruption may occur before the blisters appear. (Courtesy of the Institute of Dermatology)

Distribution

The lesions are symmetrical, often beginning on the inner thighs then spreading down the legs and involving the arms and ultimately the trunk (Fig. 19.7).

The mucous membranes are involved in a minority of patients. The blistering usually occurs within the mouth (Fig. 19.8) rather than on the lips and results in ulceration. It is possible that the patients with oral lesions have a slightly higher association with malignant disease.

There is an uncommon variant of the disease in which blisters recur in a localized (Fig. 19.9) area on the lower leg (*localized bullous pemphigoid*). Blisters may be confined to the pretibial area, a variant of bullous pemphigoid that is described in women.

Diagnosis

The pathology shows that the entire epidermis makes up the roof of the blister (Fig. 19.10), which explains why the intact vesicles or blisters are so

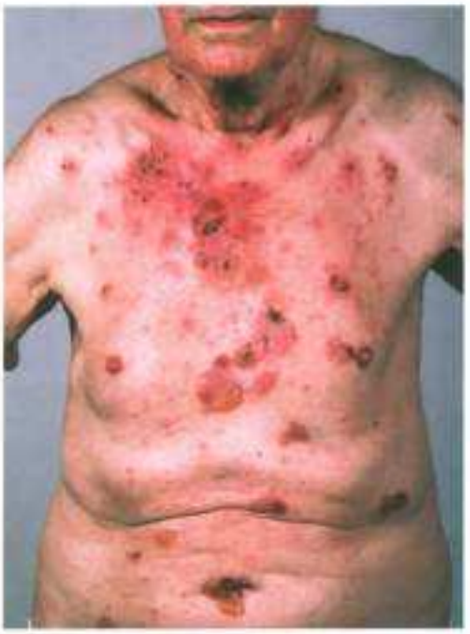


Fig. 19.7 Bullous pemphigoid. It affects the elderly and the patients often have other medical disorders. The itching and blistering are most debilitating. Potent immunosuppressives and steroids are required to induce remission.

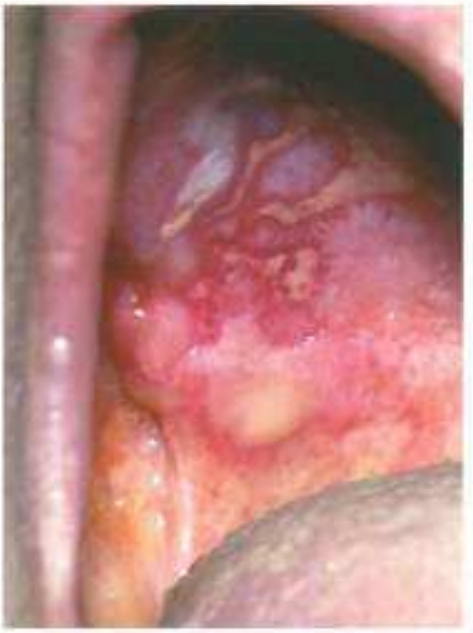


Fig. 19.8 Oral bullous pemphigoid. Blisters in the mouth are uncommon in bullous pemphigoid and may be associated with internal malignant disease.

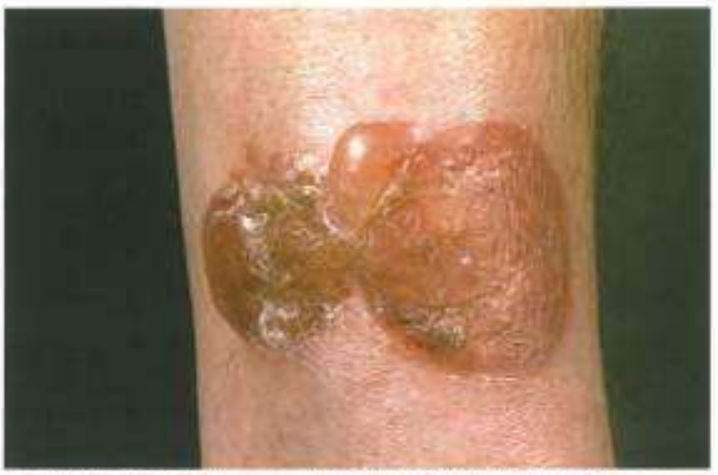


Fig. 19.9 Localized bullous pemphigoid. Intermittent bullous eruptions may occur in a localized manner, often limited to the lower leg and associated with positive immunofluorescence. Occasionally it becomes generalized.

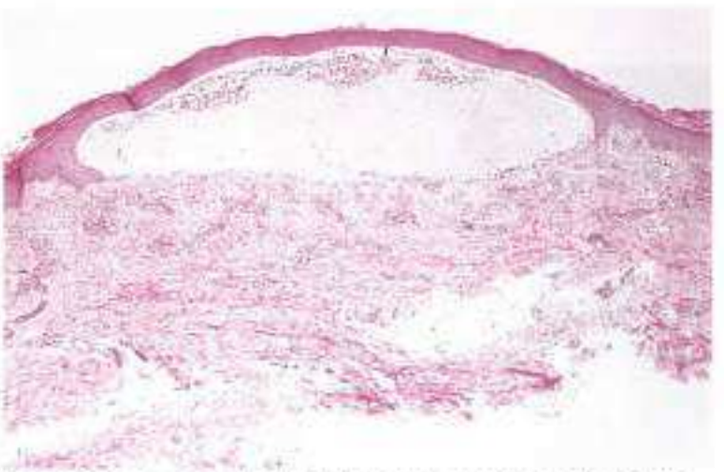


Fig. 19.10 Bullous pemphigoid. This low-power view shows an intact blister. Note that the lesion is subepidermal in location and that the cavity is unilocular.

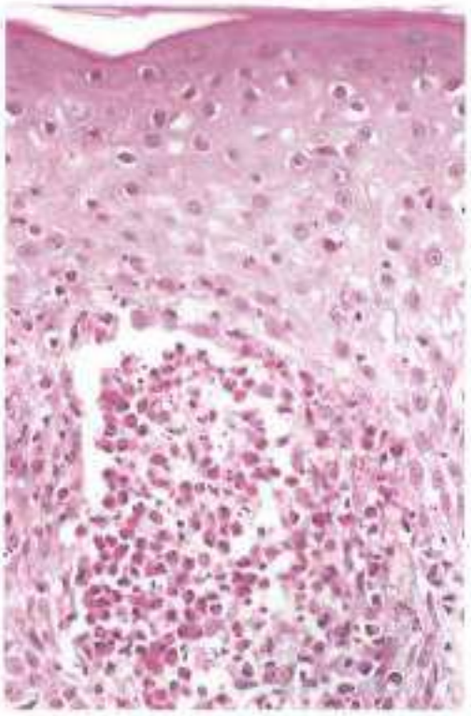


Fig. 19.11 Bullous pemphigoid. Eosinophil rich dermal papillary microabscesses are characteristic. The presence of eosinophils may suggest the diagnosis in the very itchy urticated pre-bullous stage.

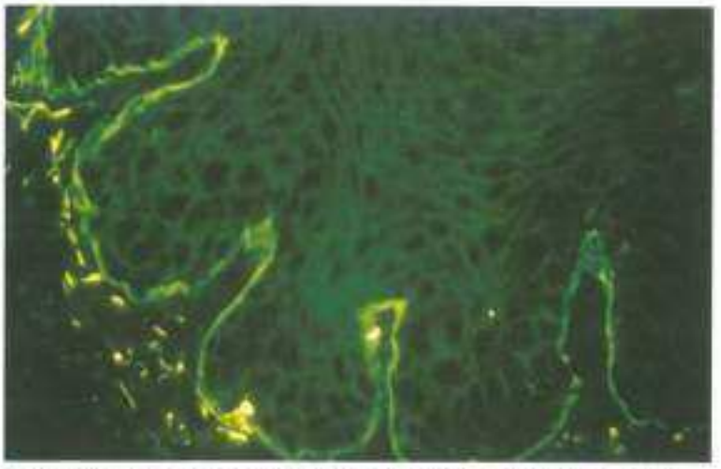


Fig. 19.12 Bullous pemphigoid: direct immunofluorescence. Fluorescein-labelled IgG and/or C3 antibodies are deposited in a linear manner on the basement membrane. The antibodies separate the epidermis from the dermis.

firm and do not break easily. There are usually many eosinophils (Fig. 19.11) within the blisters and surrounding the dermal blood vessels. The blister is subepidermal in location. Immunofluorescence is essential. The biopsy should be obtained from perilesional skin for the best results.

Almost all patients have IgG and C3 at the epidermal basement membrane zone in a linear manner (Fig. 19.12). IgG_4 is the most common subgroup. Approximately 70% have circulating antibasement membrane zone IgG antibodies, detectable by indirect immunofluorescence.

Split skin and immunoelectron microscopic techniques show that the immunoreactants are deposited within the upper portion of the lamina lucida (Fig. 19.13), unlike mucous membrane pemphigoid where they are deposited at a lower level.

Management

Diagnosis is not difficult once the blisters appear, but may be more subtle in the urticarial pre-bullous state, which may be misdiagnosed as insect bites. The intense pruritus and presence of eosinophils (see Fig. 19.11) in the biopsy should alert the astute clinician. Bullous erythema multiforme (Fig. 19.14) may cause confusion but immunofluorescence is negative.

The condition is more benign than pemphigus. However, the patients are elderly and are at risk from infection of the skin, urinary tract and lungs and from septicaemia. Deep venous thrombosis and pulmonary embolism are not uncommon. The disease may compromise coexisting disorders, especially once the patient has been started on immunosuppressive therapy.

Most patients require 40 mg enteric-coated prednisolone daily to gain control. The steroid dosage may be reduced once the blistering process has stopped (this usually takes 10 days), by 5 mg every fifth day, although maintenance is required often for several months at a dose of 12.5 mg daily. Once the patient has been maintained free of disease for 3 months, it is reasonable to reduce to 10 mg daily and then by 1 mg each week provided no fresh blisters occur. Measures to prevent steroid-induced

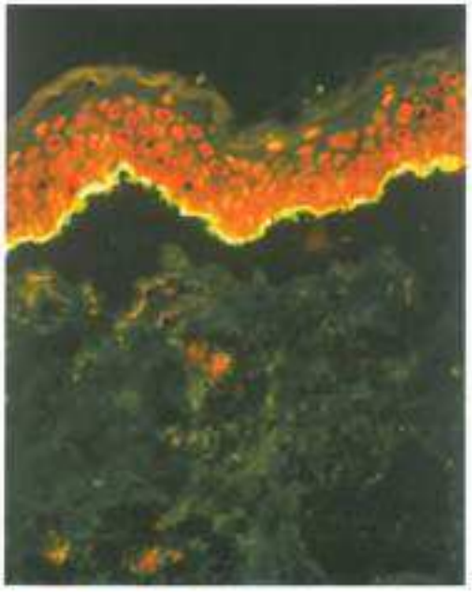


Fig. 19.13 Bullous pemphigoid. There is a noticeable gap between the epidermis and the dermis because the skin has been split by the use of sodium chloride. The antibodies (stained yellow/green) react against the epidermal side of split skin. (Courtesy of Mr Bhogal, Institute of Dermatology.)

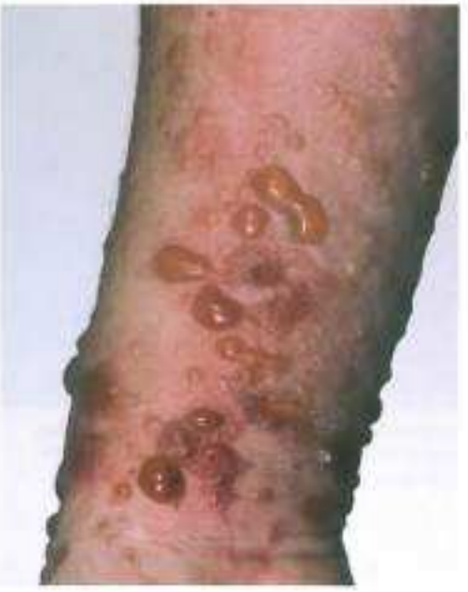


Fig. 19.14 Bullous erythema multiforme. Although many tense blisters are present, the onset of the eruption was very acute, immunofluorescence was negative and it subsided within 3 weeks.

osteoporosis should be instituted. Azathioprine, starting at 50 mg daily and then increasing up to 2 mg/kg, is thought to have a steroid-sparing effect. Patients who have genetic polymorphism in the enzyme thiopurine methyltransferase are at risk of developing leucopenia and pancytopenia and it is worth measuring this enzyme.

Other therapeutic regimens have been used, including sulphones (dapsone especially for neutrophil-predominant infiltrates in bullous pemphigoid), ciclosporin, chlorambucil, methotrexate, mycophenolate mofetil, cyclophosphamide, and tetracyclines plus nicotinamide. High-dose intravenous pulse therapy with methylprednisolone and plasmaphoresis may also be used.

Topical steroids are usually of limited value in this disease, although superpotent steroids are the treatment of choice in the rare localized variants of bullous pemphigoid. Potassium permanganate added to the daily bath is a useful local remedy.

The monitoring of the activity of the disease is controversial. Some believe that high titre anti BP180 ELISA score and to a lesser degree positive direct immunofluorescence are good predictors of continued activity and therefore potential relapse if treatment is discontinued.

Mucous membrane pemphigoid

A rare chronic mucocutaneous blistering disease that heals by scarring and is characterized by deposits of C3 and IgG in the lamina lucida of the basement membrane.

Aetiology

The alternative nomenclature of benign mucous membrane pemphigoid or ocular pemphigus is confusing. The condition is neither benign nor is it allied to pemphigus. There are similarities to bullous pemphigoid but the skin may only be involved in 20% of patients and scarring (hence a previous name, *cicatricial pemphigoid*) and involvement of the mouth, conjunctivae, anogenital mucosae and the aero-digestive tract is unusual in bullous pemphigoid. Immunofluorescence, salt-split skin techniques and the identification of target antigens has greatly clarified the situation.

A subepidermal blister is present on light microscopy. In approximately 80%, C3 and IgG are found deposited in the lamina lucida (below the hemidesmosomes of bullous pemphigoid). Circulating IgG antibodies are found in about 30%. There is an increased association with HLA-B12 phenotype. This contrasts with bullous pemphigoid, where no HLA association has yet been identified.

A subset of the mucous membrane pemphigoid has now been identified in which circulating IgG binds exclusively to the dermal side of skin split with 1 mol/l sodium chloride. This accounts for less than 10% of cases. The target antigen is laminin 332 (originally called epiligrin, kalinin or laminin 5), which is a component of anchoring filaments. These patients do not usually have laryngeal involvement. Laminin 6 may also be bound.

Clinical Features

Symptoms

This antiepiligrin form of mucous membrane pemphigoid affects predominantly the mucous membranes and there is an increased risk of non-Hodgkin's lymphoma and solid carcinomas. Ulceration of the mouth and other mucous membranes occurs, associated sometimes with blistering of the skin, usually in middle age.

Morphology

The skin may not be involved or only to a limited and occasionally widespread extent. The blisters (Fig. 19.15), which are similar to those of bullous pemphigoid and are quickly succeeded by erosions (Fig. 19.16), heal with scarring (Fig. 19.17).

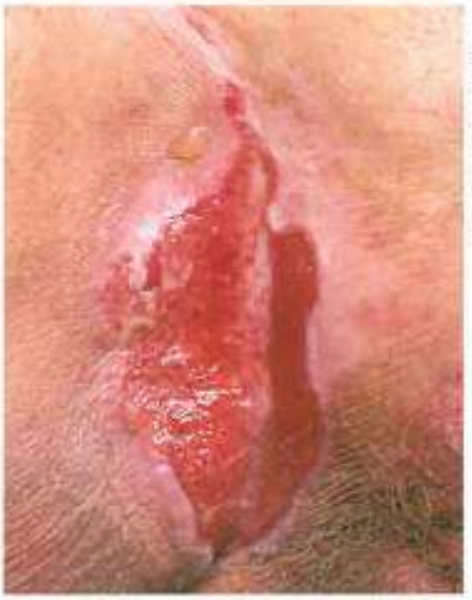


Fig. 19.15 Mucous membrane pemphigoid. The flexures may be involved. The most obvious abnormality is the large eroded area but the tense blister should suggest the cause. This patient responded to intralesional triamcinolone.

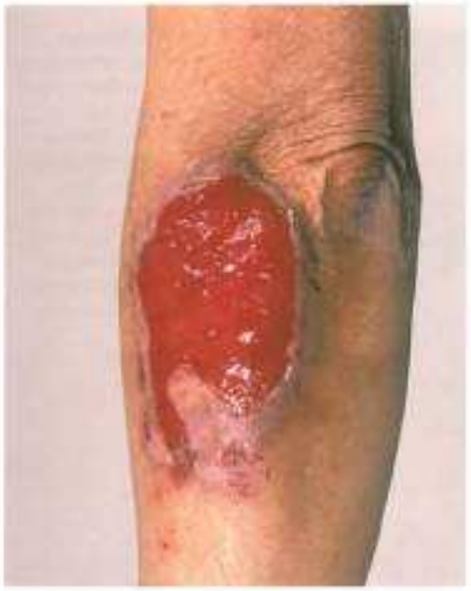


Fig. 19.16 Mucous membrane pemphigoid. The blisters are followed by red raw erosions, which are quite characteristic.

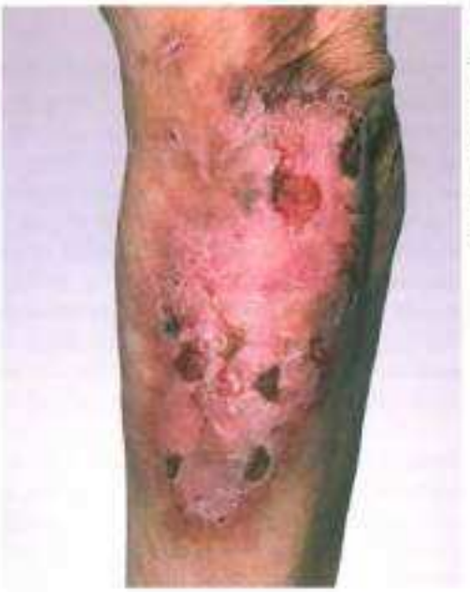


Fig. 19.17 Mucous membrane pemphigoid. The condition heals with scarring unlike bullous pemphigoid. One small blister, a frank erosion and multiple scabbed lesions are present on the background of extensive scarring.

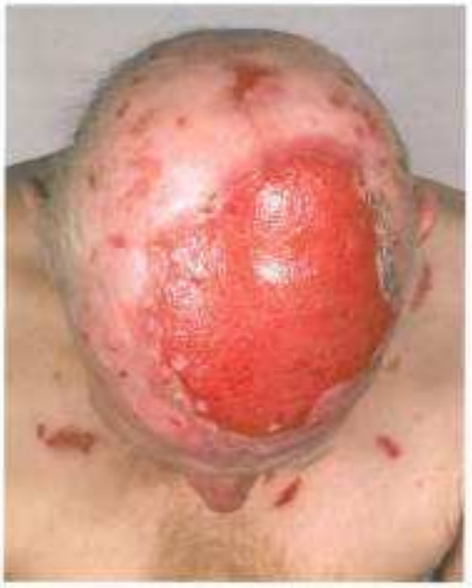


Fig. 19.18 Mucous membrane pemphigoid. There is minimal blistering with extensive erosions of the scalp (a common site). The diagnosis was confirmed by immunofluorescence.

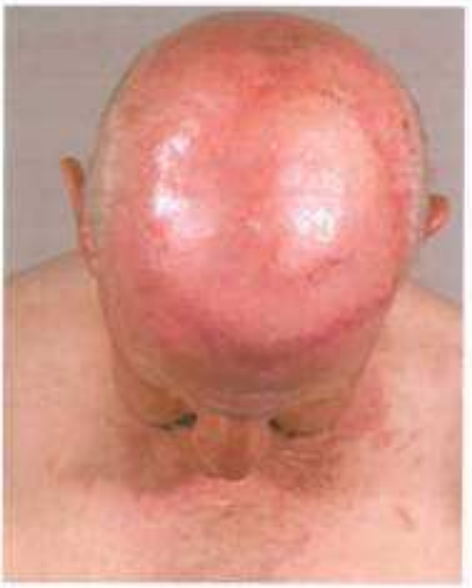


Fig. 19.19 Mucous membrane pemphigoid. This is the same patient as in Fig. 19.18. He responded to oral sulphapyridine.

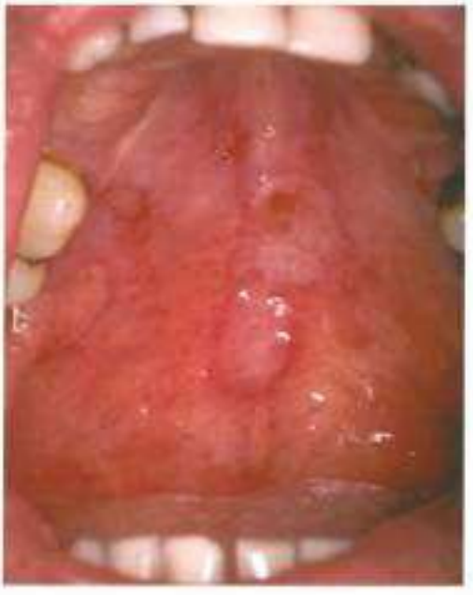


Fig. 19.20 Mucous membrane pemphigoid. Tense blisters in the mouth, which become erosions, are common.

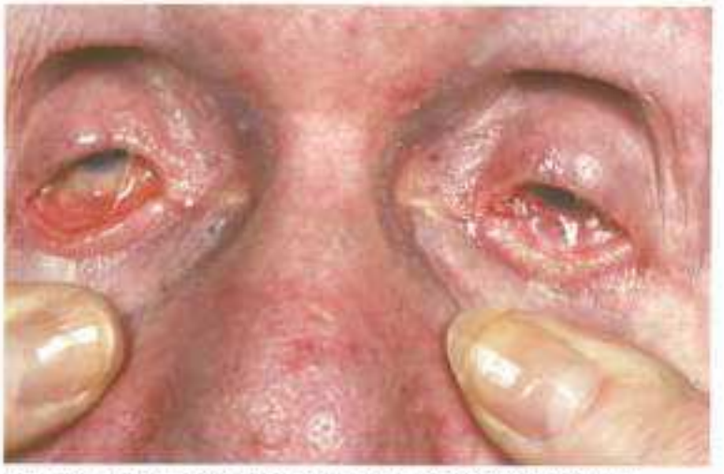


Fig. 19.21 Mucous membrane pemphigoid. Adhesions result from the blistering process between the bulbar and palpebral surfaces (symblephara). The condition may lead to blindness. (Courtesy of the late Dr R.H. Marten.)

Distribution

The face and scalp (Figs 19.18 and 19.19) are affected particularly, but also the neck, trunk and flexural areas. It is primarily a disorder of the mucous membranes, particularly the oral cavity (Fig. 19.20), nose, larynx, pharynx, oesophagus, anogenital area and, of great importance, the eyes. Involvement of the conjunctivae (Fig. 19.21) leads to fibrosis, entropion, trichiasis, symblepharon, corneal ulceration and ultimately blindness.

A variant described by Brunsting and Perry refers to intermittent crops of pruritic grouped and circumscribed blisters on the face (Fig. 19.22), scalp and neck, which heal with atrophic scars. The mucous membranes are not usually involved. The identity of the antigen is still the subject of debate and may be heterogeneous. It has been suggested that this may be a localized variant of acquired epidermolysis bullosa. It may respond to colchicine.

A pure ocular form of cicatricial pemphigoid has been described. There is immune-mediated subepithelial blistering of the mucous membrane. It is unique clinically and immunopathologically, with a low frequency of IgG and C3 deposited in vivo and no antibasement membrane antibodies detected by indirect immunofluorescence.

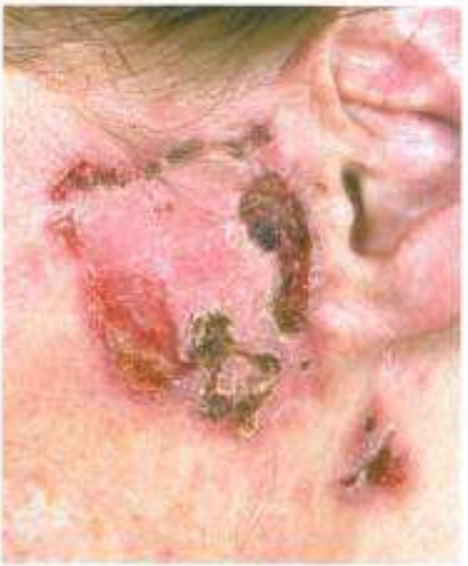


Fig. 19.22 Mucous membrane pemphigoid (Brunsting–Perry type). In front of the ear is a common site. The skin is eroded and scabbed. It heals with atrophic scarring. It is a disorder of the middle-aged and elderly. The disease is chronic and usually the blistering is confined to the face.

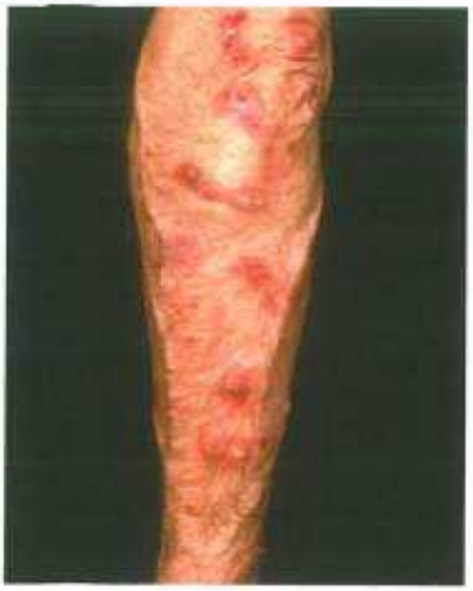


Fig. 19.23 Epidermolysis bullosa acquisita. The blisters are induced by trauma. The condition is chronic and resistant to therapy. (Courtesy of Prof. Martin Black, Department of Immunopathology, Institute of Dermatology.)

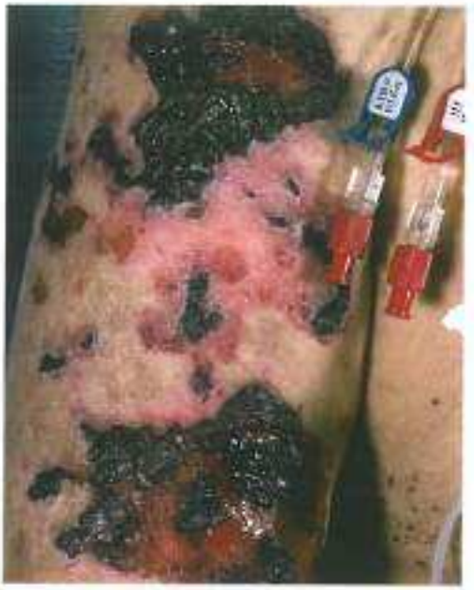


Fig. 19.24 Epidermolysis bullosa acquisita. The changes may be similar to mucous membrane pemphigoid with considerable erosions, but he had antibodies to Laminin 5. The patient also had renal failure.

Management

The ocular manifestations are characteristic. Immunofluorescent studies, of both the mucous membranes and the skin, are an absolute requirement. The management of the disease is less satisfactory than that of bullous pemphigoid. Skilled ophthalmological supervision is mandatory. Systemic steroids, other immunosuppressants (including mycophenolate mofetil and cyclophosphamide), dapsone and sulphamethoxypiridazone are used with variable success.

Epidermolysis bullosa acquisita

An acquired subepidermal autoimmune bullous disorder characterized by increased skin fragility. Type VII collagen is the target antigen.

Aetiology

Also known as *dermolytic pemphigoid*, histopathologically there are subepidermal blisters with a moderate infiltrate of neutrophils (unlike mechanobullous epidermolysis bullosa, where the infiltrate is sparse). Linear deposits of IgG are present at the basement membrane and sometimes C3, IgA and IgM. There are circulating IgG antibodies to the basement membrane zone in about 50%. Immunoelectron microscopy has shown that the antibodies are below the lamina lucida in the lamina densa, in contrast to bullous pemphigoid which involves the lamina lucida. The salt-split skin technique also shows that bullous pemphigoid antibodies react to the epidermal side of the split skin whereas the antibodies in epidermolysis bullosa acquisita react to the dermal side. The target antigen is the globular amino-terminal non-collagenous domain of type VII collagen. It is found only in anchoring fibrils. In epidermolysis bullosa acquisita, immune complexes are found within the lower portions of the lamina densa and sublamina densa zones of the dermo-epidermal junction (where the anchoring fibrils are situated). By comparison, in bullous pemphigoid, the antibodies bind to a non-collagenous glycoprotein in the hemidesmosomes of the basal cell and the upper lamina densa space. Immunogold and immunoblotting techniques show that antibodies in epidermolysis bullosa acquisita recognize 290 and 145 kDa antigens that are identified as collagen VII.

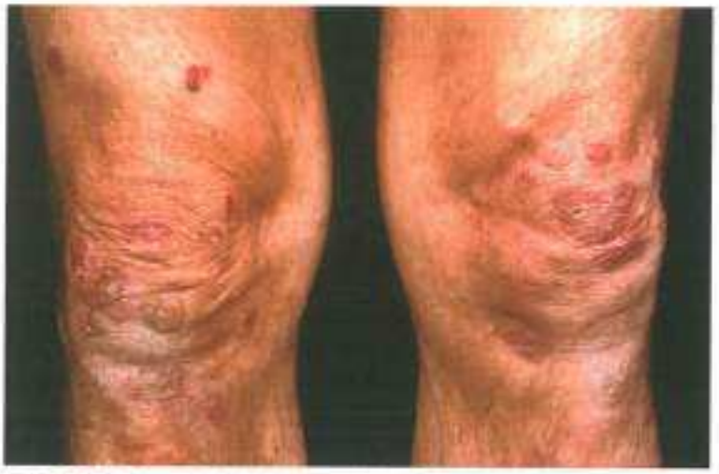


Fig. 19.25 Epidermolysis bullosa acquisita. The skin is fragile and the blisters are induced by trauma. (Courtesy of Prof. Martin Black.)

It may occur in any age group and there is an association with amyloid, inflammatory bowel disease, multiple myeloma, lymphoma, lupus erythematosus, thyroiditis and diabetes mellitus.

Clinical Features

Symptoms

There is skin fragility and itchy blisters.

Morphology

It resembles either bullous pemphigoid or the dystrophic form of epidermolysis bullosa, with mucous membrane changes similar to mucous membrane pemphigoid. There may be widespread inflammatory blisters (Fig. 19.23), as in bullous pemphigoid. Erosions may be prominent (Fig. 19.24). The blisters (Fig. 19.25) heal with scarring and/or milia formation (Fig. 19.26). There may be mutilation of the fingers and hands.

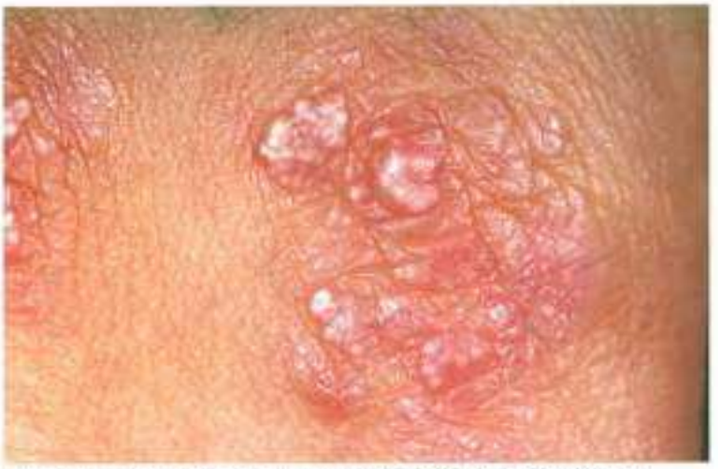


Fig. 19.26 Epidermolysis bullosa acquisita. The blisters heal with milia formation, a characteristic of dermo-epidermal junction blistering disorders. This 25-year-old also had Crohn's disease.

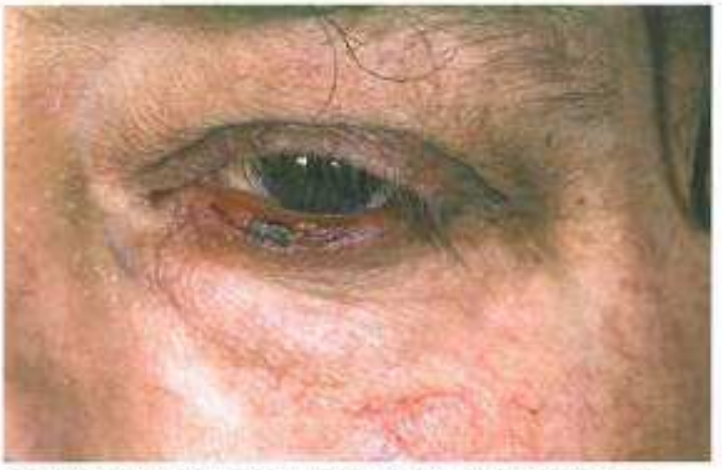


Fig. 19.27 Epidermolysis bullosa acquisita. This is the same patient as in Figure 19.24. The involvement of the eyes suggests cicatricial pemphigoid but the immunogold technique demonstrated antibodies against collagen VII.

Distribution

The blisters are found in acral areas and extensor surfaces. The mucous membranes of the mouth, nose, eyes (Fig. 19.27), pharynx or larynx are involved, either all or in part. The nails are dystrophic.

Management

Diagnosis is confirmed by immunofluorescence using the split-skin technique (Fig. 19.28) and by immunoelectron microscopy, where the IgG is found deposited in the upper dermis beneath the basal lamina within the sublamina densa.

Local steroids may be helpful but the condition is largely resistant to treatment with parenteral agents including systemic steroids. Azathioprine, dapsone, mycophenolate mofetil, rituximab, intravenous immunoglobulin, ciclosporin and extracorporeal photophoresis have been used.

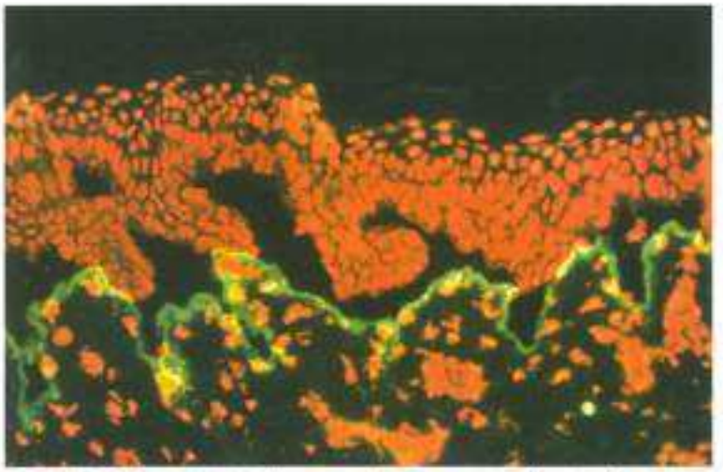


Fig. 19.28 Epidermolysis bullosa acquisita. A gap caused by 1 mol/l sodium chloride is seen between the epidermis (where the cells are stained orange) and the dermal side of the basement membrane, where the antibodies are stained green. (Courtesy of Mr B. Bhogal, Institute of Dermatology.)

Pemphigus

Pemphigus includes a set of rare autoimmune intraepidermal blistering disorders that may affect the skin and mucous membranes. The histopathological hallmark of these diseases is acantholysis, which is a disruption of the normal cell-to-cell adhesion in the epidermis. The term pemphigus is derived from the Greek word *pemphix*, which means bubble. It was originally employed to include all blistering diseases. Beutner and Jordan, in 1964, showed that the serum in pemphigus contained autoantibodies to an intercellular substance. There are a number of variants, some of which are more serious than others, but all are united by the finding in vivo of circulating and bound IgG antibodies directed against antigen on the surface of keratinocytes.

Desmosomes connect one keratinocyte to another via cell adhesion molecules of the cadherin family. There are two families of cadherins: desmogleins and desmocollins. Antibodies against these adhesion molecules cause the acantholysis of pemphigus. In desmosomes, there are keratin filaments that link to plakin proteins, which are found just under the plasma membrane, and to the transmembrane proteins that are known as desmogleins. These filaments connect to the desmogleins, plakins and keratin of the adjacent cell. There are three immunological forms of pemphigus with several clinical variants, usually targeted by IgG but occasionally by IgA autoantibodies. In pemphigus foliaceus, there are antibodies against desmoglein 1 (Dsg 1). In the variety of pemphigus vulgaris that is limited to the oral mucosa, there are antibodies against desmoglein 3 (Dsg3, a 130 kDa glycoprotein), and in the form of pemphigus vulgaris that affects both

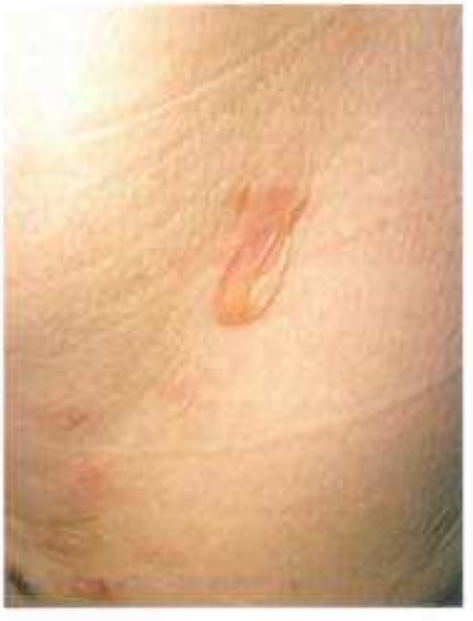


Fig. 19.29 Pemphigus vulgaris. The blisters are superficial and flaccid, in contrast to the tense blisters of pemphigoid. (Courtesy of Prof. L. Fry, St Mary's Hospital, London.)

the mucosa and the skin, there are antibodies against desmogleins 1 and 3. In paraneoplastic pemphigus, a broader range of desmosomal proteins are involved, including plakins, desmoglein 3 and desmoglein 1.

Pemphigus vulgaris

A serious mucocutaneous autoimmune disorder of intraepidermal cell cohesion, resulting in flaccid blisters and painful erosions.

Aetiology

Pemphigus vulgaris is a rare autoimmune disorder, strongly associated with HLA-DR4, which is most common in Jews and Indians. There is an association with other autoimmune diseases, such as rheumatoid arthritis, pernicious anaemia, Sjögren's syndrome, thymoma and myasthenia gravis, in the patient or family members. The IgG antibodies are directed against the intercellular cement substance and can be demonstrated by direct or indirect immunofluorescence. Fragile blisters result; in pemphigus vulgaris, the split is low in the epidermis (suprabasal) and erosions are the prominent physical sign. In other varieties of pemphigus, for example pemphigus foliaceus, the split is more superficial (subcorneal) and crusting is more pronounced. In pemphigus vulgaris, there are antibodies against desmoglein 3, which causes the acantholysis in the oral cavity (mucosal pemphigus vulgaris). If epitope spreading (a phenomenon of autoimmunity) occurs, antibodies form also against desmoglein 1 (mucocutaneous pemphigus vulgaris).

Clinical Features

Symptoms

Painful sores in the mouth, other mucous membranes and skin.

Morphology

Blisters are flaccid (Fig. 19.29), in contrast to the tense and firm blisters of pemphigoid, and may arise on normal or erythematous skin. They break easily (Fig. 19.30) and form erosions (Fig. 19.31), which heal slowly, often with crusting and subsequently postinflammatory hyperpigmentation but without scarring. Extensive denudation of the skin may occur. Polycyclic lesions (Fig. 19.32), with blistering evident at the margins (Fig. 19.33), may be present. Because epidermal cell cohesion is damaged, on examination the upper layer of the epidermis may be made to slide over the lower using the finger (Nikolsky's sign).

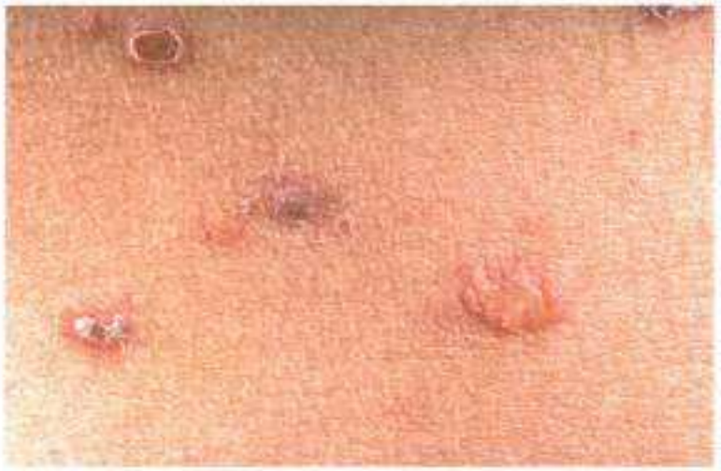


Fig. 19.30 Pemphigus vulgaris. The blisters are superficial and the roof of each blister is quickly detached leaving painful erosions behind (Fig. 19.31).

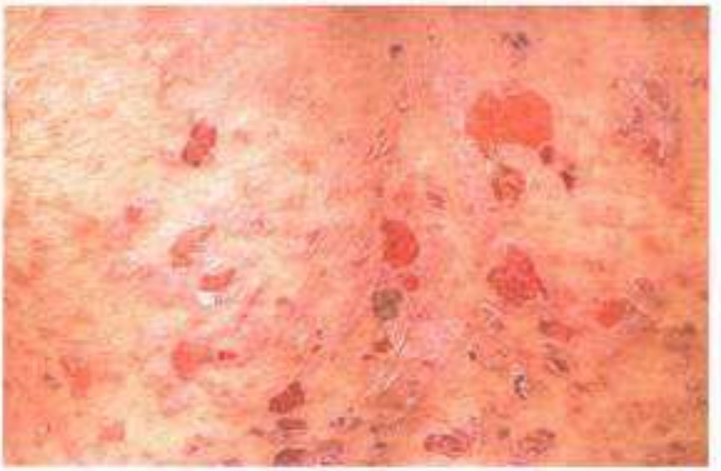


Fig. 19.31 Pemphigus vulgaris. The blisters break easily and erosions result, which are painful and heal slowly as in this 34-year-old patient from the Middle East.

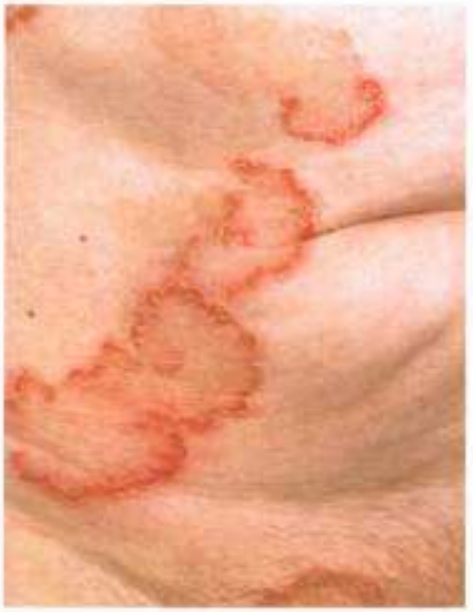


Fig. 19.32 Pemphigus vulgaris. Polycyclic lesions may occur with superficial blistering and peeling evident at the margins.

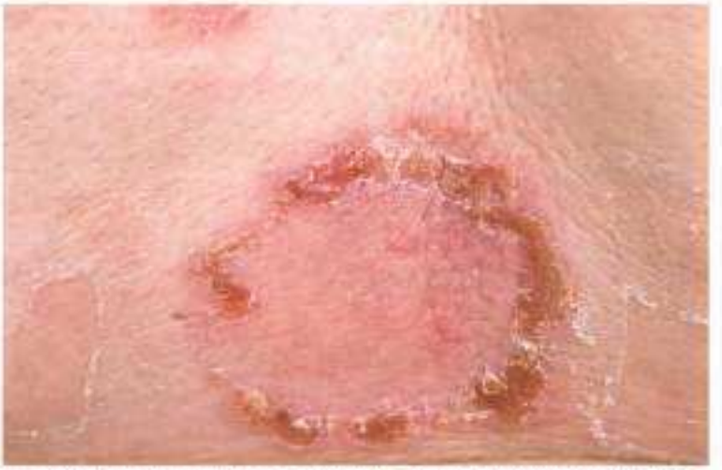


Fig. 19.33 Pemphigus vulgaris. Annular lesions may be present, with blistering and crusting evident at the margins.

Distribution

The axilla, umbilicus (Fig. 19.34), trunk (Fig. 19.35), scalp (Fig. 19.36) and face are usually involved, but any area of skin can be affected.

In half the patients the disorder starts in the mouth with flaccid blisters that result in painful erosions (Fig. 19.37) and affect primarily the buccal mucous membranes (Fig. 19.38), palate, gingiva and tongue (Fig. 19.39). However, all stratified squamous epithelial mucosal surfaces may be involved, including the pharynx, larynx, oesophagus, conjunctivae, urethra, vulva, penis (Fig. 19.40), cervix and rectum.

Diagnosis

The diagnosis may be confirmed by a skin biopsy. There is oedema and disappearance of the epidermal intercellular bridges in the lower epidermis initially and often within the adnexal structures. This gives rise to acantholysis (Fig. 19.41). Subsequently, suprabasal intraepidermal blisters occur. Some patients have focal collections of eosinophils within the epidermis in addition, an appearance that is known as *eosinophilic spongiosis*.

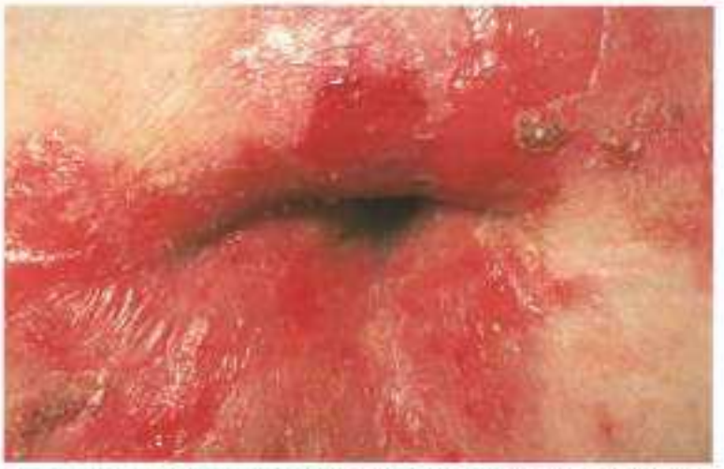


Fig. 19.34 Pemphigus vulgaris. The blisters result in raw, tender, denuded and eroded skin. The umbilicus is a common site.

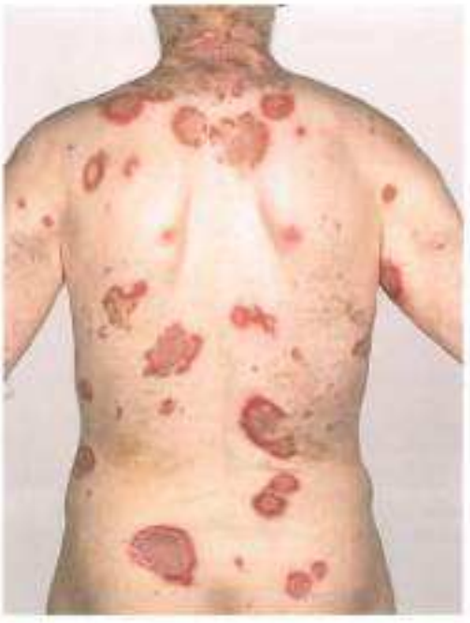


Fig. 19.35 Pemphigus vulgaris. The disease usually affects the mucosae first with antibodies against Dsg3. 50% also have antibodies to Dsg1 and the skin is involved. The eruption eventually becomes extensive and, prior to the advent of steroids, most patients died, usually from infection.

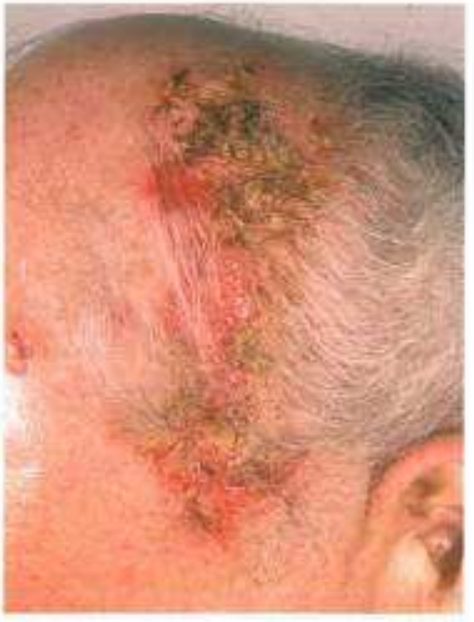


Fig. 19.36 Pemphigus vulgaris. Flaccid, blistering erosions and crusting are present on the scalp. A biopsy for histology and immunofluorescence will make the diagnosis.

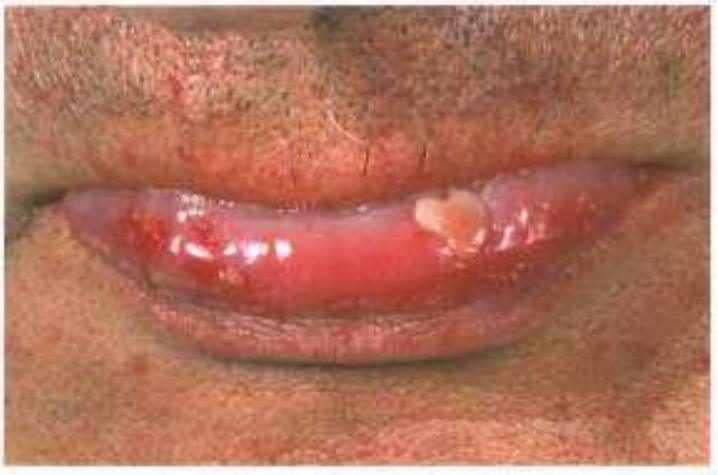


Fig. 19.37 Pemphigus vulgaris. There are persistent blisters and erosions on the tongue that fail to heal.

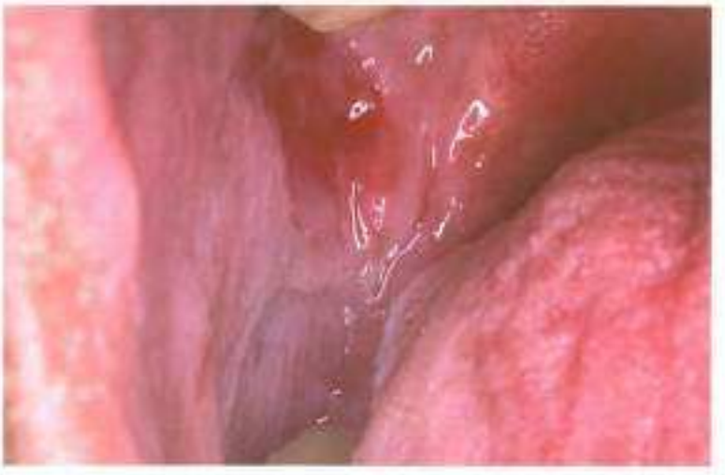


Fig. 19.38 Pemphigus vulgaris. The disorder often starts in the mouth. Blisters may be seen but erosions are more common. They are very painful and slow to heal.

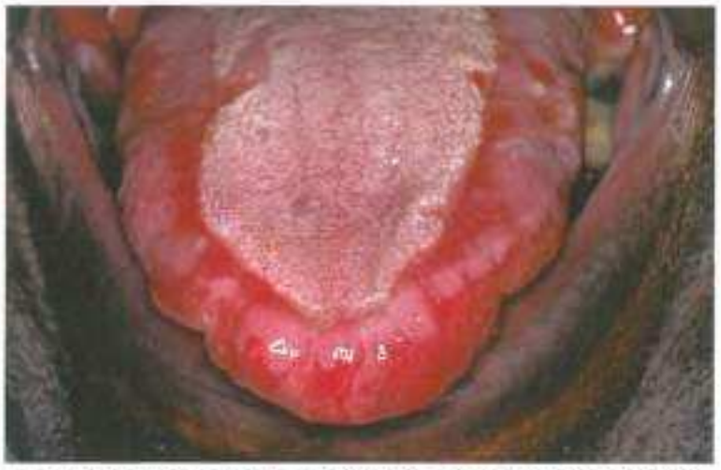


Fig. 19.39 Pemphigus vulgaris. The tongue has become extensively denuded in this patient. Eating becomes a major problem because of the pain.

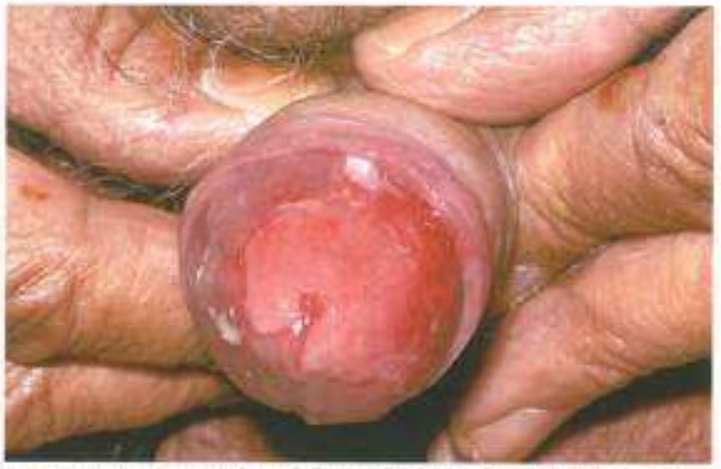


Fig. 19.40 Pemphigus vulgaris. The first sign may be raw, painful, denuded erosions on the genitalia. (Courtesy of the Institute of Dermatology.)

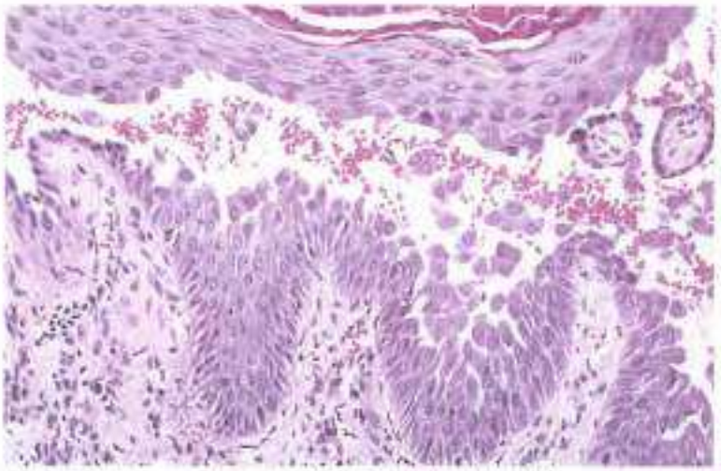


Fig. 19.41 Pemphigus vulgaris. The blister is intraepidermal, formed by loss of intercellular bridges between adjacent keratinocytes (acantholysis). A scattered chronic inflammatory cell infiltrate is present in the papillary dermis.

Fig. 19.42 Pemphigus vulgaris. The green stain shows deposits of IgG between the epidermal cells. The nuclei are a red-orange colour because of the use of a counter stain. (Courtesy of Mr B. Bhogal.)

Under the electron microscope, it is seen that the desmosomes gradually disappear and there is retraction of the tonofilaments to the perinuclear area, with subsequent degeneration of the acantholytic cells. The hemidesmosomes are not affected since they do not include intercellular cement substance; consequently, the basal keratinocytes remain attached like 'tombstones' to the basement membrane.

Linear deposits of IgG may be demonstrated between the epidermal cells in all patients during active disease (Fig. 19.42). Approximately half also have C3, and a minority have IgM and IgA. These findings are best seen in biopsies taken from perilesional skin. It should be noted that these antibodies are not specific for they have been found in individuals without pemphigus vulgaris, for example in those with burns. The majority of patients manifest IgG circulating antibodies against the intercellular cement substance and this can be helpful in the management of the disease in that the disease activity often correlates quite well with the antibody titre. Exfoliative cytology may also be useful in diagnosis, particularly of lesions in the mouth (the Tzanck test). Acantholytic cells are demonstrable (Fig. 19.43). Many patients have an eosinophilia.

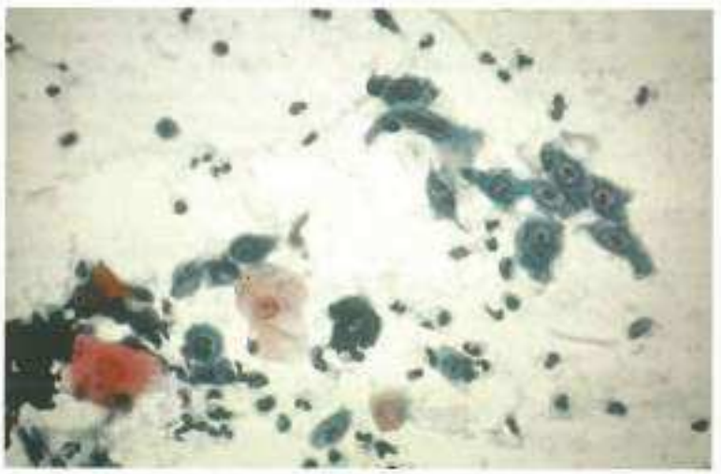


Fig. 19.43 Pemphigus vulgaris. The individual keratinocytes, which have been separated by acantholysis, are demonstrable by exfoliative cytology (Tzanck test).

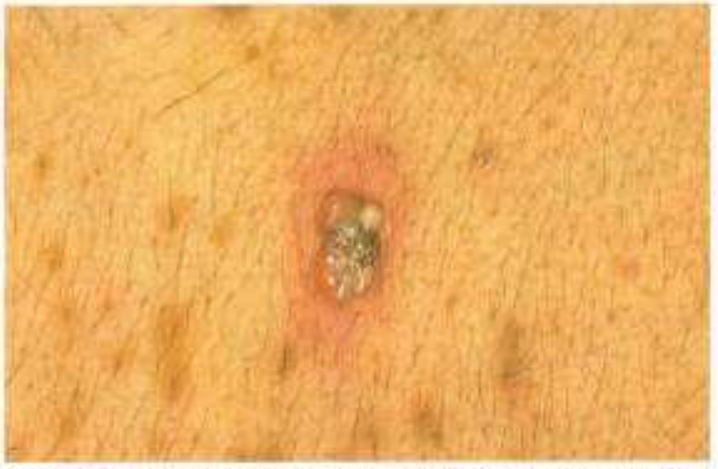


Fig. 19.44 Pemphigus vegetans. Besides the vesicles there are pustules which are characteristic of the Hallopeau type, which has a relatively benign course.

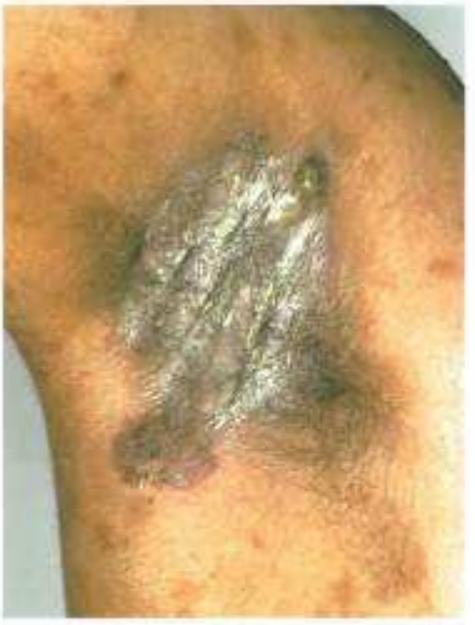


Fig. 19.45 Pemphigus vegetans. There is increased immunological resistance to the disease and the blisters heal with hypertrophic, warty and vegetative masses, especially in the flexures. (Courtesy of the late Dr R. H. Marten.)

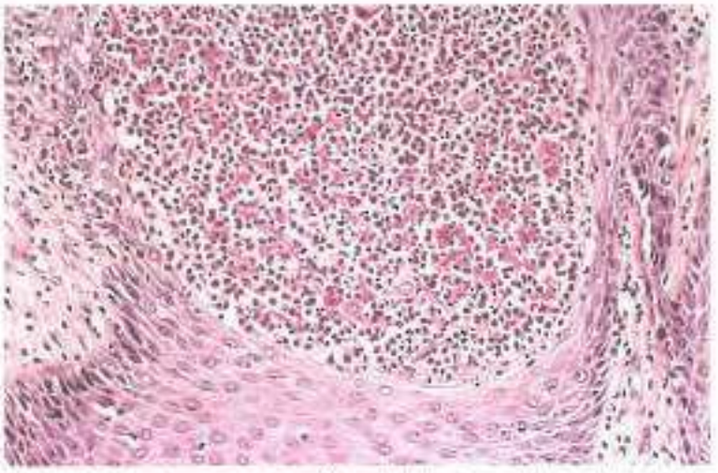


Fig. 19.46 Pemphigus vegetans. Although similar to pemphigus vulgaris in that suprabasal acantholysis is present, this is often masked, as here, by intraepidermal abscess formation with conspicuous eosinophilia.

Immunofluorescence does have its limitations in that the lace- and wire-like pattern is seen not only in pemphigus vulgaris but also in pemphigus foliaceus and in paraneoplastic pemphigus. Immunoprecipitation and immunoblotting techniques are laborious and only available in certain laboratories, but can distinguish them. However, the cloning of *DSG 3*, the gene for desmoglein 3, has permitted the in vitro production of recombinant desmoglein 3 antigen. This is now a standard sensitive enzyme-linked immunosorbent assay (ELISA) specific for pemphigus vulgaris.

PEMPHIGUS VEGETANS

The rarest variant of pemphigus vulgaris and characterized by antibodies against the 130 kDa target antigen and flaccid blisters, which heal to produce warty masses, particularly in the flexures.

Aetiology

The terms Neumann type (associated with an aggressive course) and Hallopeau type (less severe with remissions after treatment) are virtually abandoned. It is possibly related to an increased immunological resistance to the disease. The major histological feature is of suprabasal acantholysis. As the lesions progress, pseudoepitheliomatous hyperplasia, hyperkeratosis and papillomatosis are seen. Intraepidermal abscesses composed predominantly of eosinophils are usually present and are considered almost diagnostic of pemphigus vegetans. The immunofluorescent changes are identical to those in pemphigus vulgaris.

Clinical Features

Symptoms

Painful mouth ulceration and cutaneous blisters which give rise to warty masses, particularly in the flexures.

Morphology

The disorder starts in a similar manner to pemphigus vulgaris with flaccid blisters (Fig. 19.44) that break easily; however, as they heal, hypertrophic, warty and vegetative masses occur (Fig. 19.45). Sometimes, pustules are to be seen around previously ruptured blisters.

Distribution

Flexural locations predominantly. The groin, axillae, perineum and the mouth are affected, including the vermilion border of the lips. A cerebriform appearance of the tongue may be present.

Diagnosis

A skin biopsy must be performed for routine histology (Fig. 19.46) and immunofluorescence.

PEMPHIGUS FOLIACEUS

A subcorneal acantholytic blistering disorder characterized by autoantibodies against desmoglein 1 which occurs in idiopathic, epidemic or drug-induced forms.

Aetiology

Most cases are idiopathic although like other forms of pemphigus there may be a personal or family history of related autoimmune diseases. There is, however, a distinctive endemic variety that occurs in rural South America and in particular Brazil. It affects children, adolescents or young adults. It is known as *fogo selvagem*, which means wildfire in Portuguese. The disorder disappears from endemic areas as jungle is cleared. It may be caused by a virus. In particular, thymosin alpha 1, a thymic polypeptide associated with certain established viral infections, is raised. This finding is unique to this variety of pemphigus.

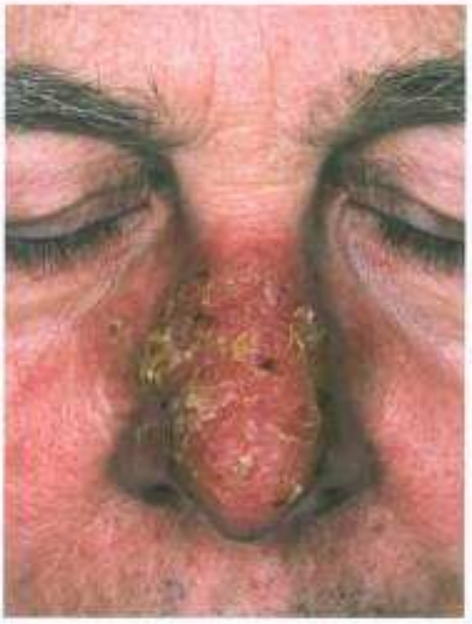


Fig. 19.47 Pemphigus foliaceus. The skin is red, raw and crusted across the nose. This is a difficult diagnosis clinically, although these appearances are typical. A biopsy will suggest the diagnosis and immunofluorescence will confirm it.

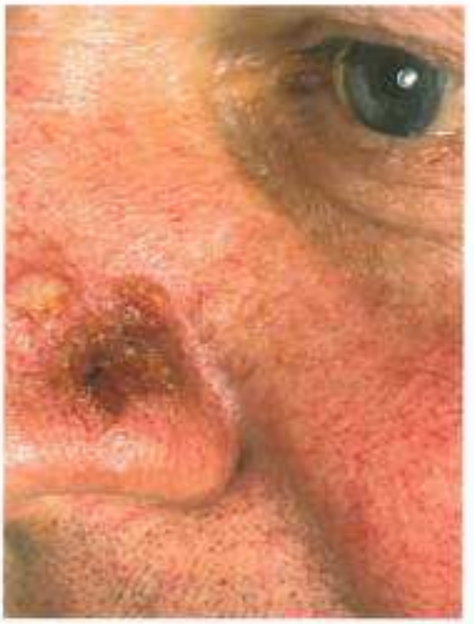


Fig. 19.48 Pemphigus foliaceus. The ala nasi are often involved. Note the small purulent blister that was the clue to the diagnosis.

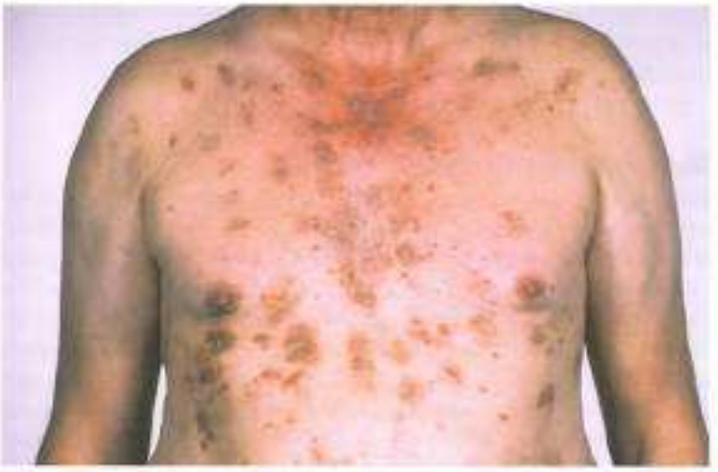


Fig. 19.49 Pemphigus foliaceus. Superficial crusting rather than blistering predominates. The chest is commonly affected. The target antigen is desmoglein 1.

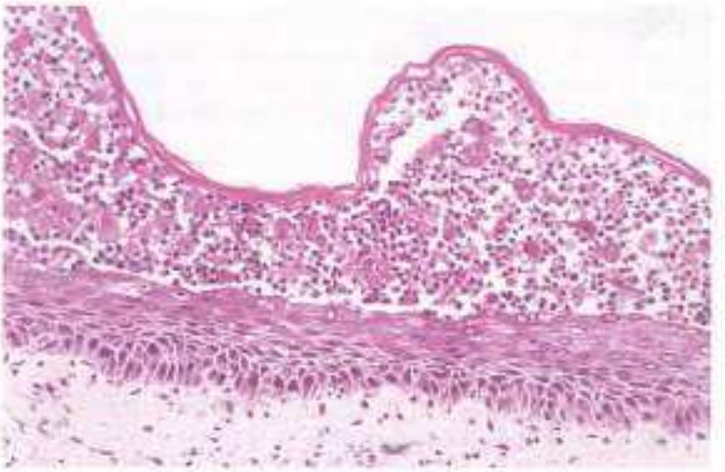


Fig. 19.50 Pemphigus foliaceus. The blister is situated immediately below the stratum corneum. In addition to neutrophils and scattered eosinophils, it contains numerous acantholytic keratinocytes.

In a small proportion of patients, the disorder is drug induced. Penicillamine is most frequently implicated, although piroxicam, penicillin, captopril, rifampicin and phenobarbital have been reported to induce a pemphigus-like eruption. The pattern resembles pemphigus foliaceus, rather than other types of pemphigus. A number of patients with penicillamine-induced eruptions have an increased frequency of *HLA-B15*, which suggests that the penicillamine may unmask a genetic predisposition to the development of pemphigus antibody.

The target antigen is desmoglein 1, which is expressed mostly in the upper levels of the epidermis. The blistering is, therefore, in and around the granular cell layer. Dsg1 is also present in oral epithelium, but oral lesions are unusual in pemphigus foliaceus because Dsg3 is also present in the superficial oral epithelium and can protect the cells from detaching.

Clinical Features

Symptoms

There is often severe itching, sometimes burning.

Morphology

Recurrent superficial erosions occur, together with erythema, scaling and crusting (Fig. 19.47). Intact flaccid blisters are rarely observed (Figs 19.48 and 19.49). The Nikolsky sign is a helpful positive physical finding.

Distribution

The face, scalp, chest and back (rather like seborrhoeic dermatitis) are affected. Eventually it spreads further. Oral lesions are practically never seen.

Diagnosis

The endemic and drug-induced varieties are easily separated from the idiopathic type. The histology shows a subcorneal acantholytic blister (Fig. 19.50). Direct immunofluorescence of perilesional skin shows IgG and C3 deposited intercellularly, just as in pemphigus vulgaris. Circulating IgG autoantibodies are usually present.

PEMPHIGUS ERYTHEMATOSUS

An autoimmune blistering disorder with clinical and immunological features of pemphigus foliaceus and lupus erythematosus.

Aetiology

Also known as the *Senear–Usher syndrome*, the histology reveals subcorneal blistering and acantholysis that is identical to that in pemphigus foliaceus. Indirect immunofluorescence shows IgG and C3 deposited in a linear manner in the intercellular spaces and in a granular fashion at the dermo-epidermal junction. The majority have a circulating intercellular substance antibody and over half have circulating antinuclear antibodies. Most do not, however, develop systemic lupus. Some have a thymoma and myasthenia gravis and remit following thymectomy. It occurs at all ages.

Clinical Features

Symptoms

The rash may be exacerbated by sunlight.

Morphology

Superficial blistering, erythema, scaling and crusting of the skin occur (Fig. 19.51).

Distribution

The nose and cheeks are affected, reminiscent of the butterfly distribution of lupus erythematosus. The upper back, chest (Fig. 19.52) and intertriginous areas can also be affected. The mouth is not affected.

Diagnosis

The histology and immunofluorescence are identical to that of pemphigus foliaceus. The antinuclear factor and granular deposition of immunoglobulins at the dermo-epidermal junction distinguish the condition from other forms of pemphigus.

RARE VARIANTS OF PEMPHIGUS

Pemphigus herpetiformis (acantholytic herpetiform dermatitis) is characterized by severe pruritus and erythematous urticarial plaques and vesicles occurring in a herpetiform arrangement. Oral lesions may or may not be present. The clinical features are of dermatitis herpetiformis but the immunology is that of pemphigus with IgG antibodies against the keratinocyte cell surfaces. They are mostly antidesmoglein 1. Some are antidesmoglein 3. The histology is variable, with eosinophilic spongiosis, subcorneal pustulosis and minimal or no apparent acantholysis. This variant has a tendency to respond to sulphones.

Pyodermatitis-pyostomatitis vegetans has similar mucocutaneous and histopathological features to pemphigus vulgaris, but negative immunofluorescence. It is associated with ulcerative colitis and occasionally Crohn's disease.

Paraneoplastic pemphigus has an insidious onset and runs a chronic course. There is usually an intractable stomatitis that is resistant to therapy, painful mucosal ulceration and blisters. The oropharynx and vermilion border of the lips are also involved. There may be a pseudomembranous conjunctivitis. The skin lesions are polymorphic, sometimes lichenoid, papules, which become blisters and erosions and target-like particularly on the trunk and extremities (including the palms and soles). There may be painful and debilitating ulcerative paronychial lesions. The associated neoplasms include all forms of lymphoma, chronic lymphatic leukaemia, thymomas (benign and malignant) and Castleman's tumour. Host antibodies to tumour antigens cross-react with plakins (intercellular adhesion molecules). Histologically, there is a vacuolar interface abnormality with keratinocyte necrosis and intraepidermal acantholysis (a cardinal feature). IgG and C3 are found within the intercellular spaces of the epidermis and there is a granular linear deposition of complement in the basement membrane. Serum autoantibodies bind to cell surfaces of the skin and mucosa, as in pemphigus. These antibodies recognize a variety of desmosome and hemidesmosome target antigens.

IgA pemphigus is described below.

Management of Pemphigus

The prognosis depends on the age of the patient, the extent and type of the disease and the doses of systemic steroids required to control it. These drugs seem to act by decreasing autoantibody levels. Anti-Dsg1 antibody ELISA values do correlate with disease activity, but anti-Dsg3 do not. The disorder was usually fatal prior to the introduction of systemic steroids, steroid-sparing immunosuppressive agents and improved supportive measures. The commonest causes of death are pulmonary embolus and infection. High doses of systemic glucocorticosteroids (for example 80 mg prednisolone) are used initially and gradually reduced as the blisters cease appearing; they are combined with other immunosuppressant agents such as methotrexate, cyclophosphamide, azathioprine or ciclosporin. Other agents, such as gold or dapsone, and plasmapheresis have also been used. Some of these agents may be used without systemic steroids in less severe

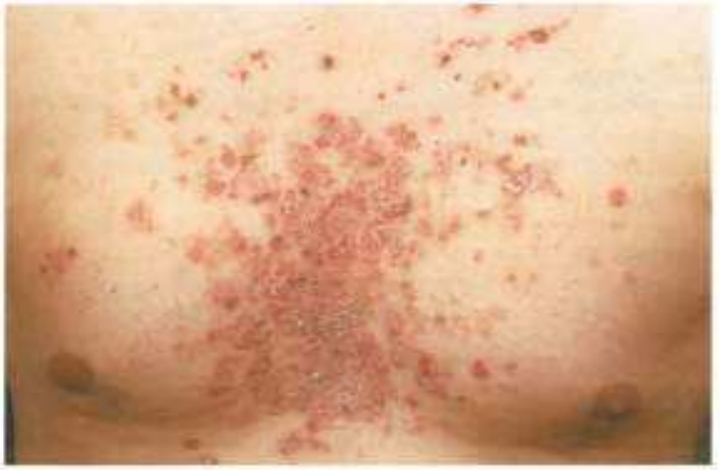


Fig. 19.51 Pemphigus erythematosus (Senear–Usher syndrome). Superficial blistering, erosions and crusting occur as in pemphigus foliaceus, to which it is identical clinically although more localized.

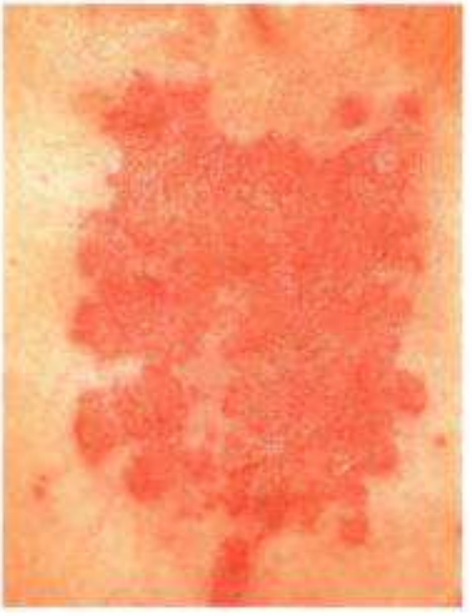


Fig. 19.52 Pemphigus erythematosus (Senear–Usher syndrome). The sternum is a common site. The histology is identical to pemphigus foliaceus, but immunofluorescent changes of both pemphigus and lupus occur. The antinuclear factor is positive.

disease. The usual regimen is gold, in the form of myocrisin given intramuscularly starting at 10 mg and then increasing by 25 mg to 50 mg once weekly. The urine and full blood count need to be closely monitored.

Azathioprine was the standard agent, but was being replaced by mycophenolate mofetil, which selectively inhibits inosine monophosphate dehydrogenase, a key enzyme in the de novo synthesis of purines and a critical step in lymphocyte proliferation. However, rituximab (MabThera), an anti-CD20 antibody is proving to be highly effective, and may replace systemic steroids and other immunosuppressants.

The oral lesions may be helped by the use of Neoral (oral ciclosporin) 1 ml diluted with 5 ml of apple juice and held locally within the mouth for several minutes and then spat out.

Clearly patients with drug-induced pemphigus should have the drug discontinued. Most patients recover spontaneously but may need systemic steroids to cover them while they respond.

Severe pemphigus must be managed in hospital. Skilled nursing care, with attention to oral toilet, wet dressings to the skin, ripple beds and constant turning of the patient to prevent bed sores, is essential. A vigilant watch must be kept for infection of the skin and other sites, and for the side-effects of systemic steroids.

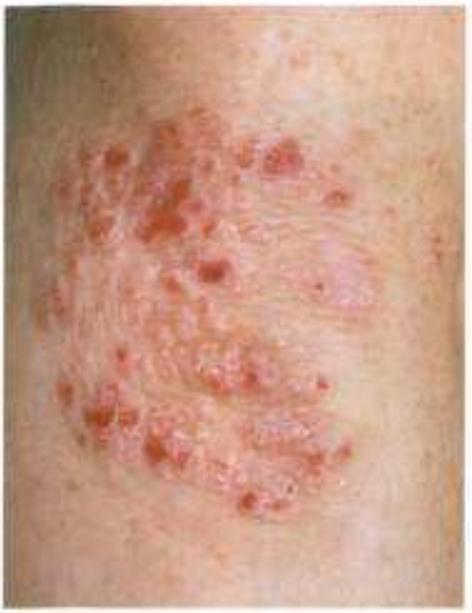


Fig. 19.53 Dermatitis herpetiformis. The vesicles are intensely pruritic, occur in groups (hence herpetiform) and are readily excoriated. These were on the elbow.

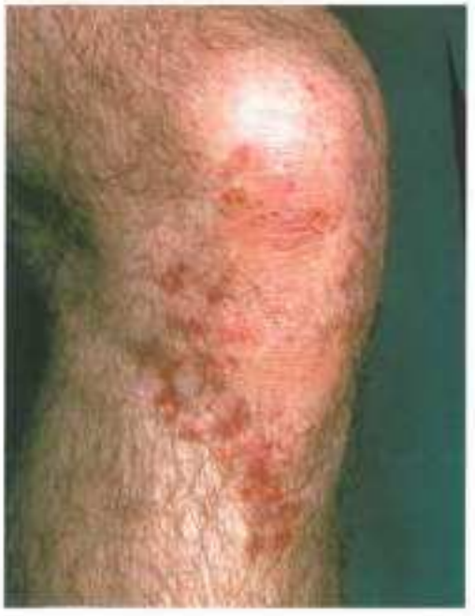


Fig. 19.54 Dermatitis herpetiformis. Excoriated vesicles occur over the fronts of the knees and lower legs. (Courtesy of St Mary's Hospital, London.)

Dermatitis herpetiformis

A pruritic condition of grouped vesicles localized to certain areas of the body associated with gluten-sensitive enteropathy and deposits of IgA in the skin.

Aetiology

Dermatitis herpetiformis is rare. It is not seen in black or Japanese patients but occurs in Europe, particularly in the Irish. There may be a family history of coeliac disease or even of dermatitis herpetiformis. There is an increased incidence of *HLA-D3* and *HLA-DQw* genotypes. It is associated with other autoimmune diseases such as Graves' disease and pernicious anaemia. It occurs in both sexes and usually commences in the second or third decade but may start at any time, including childhood. It is persistent, although it may be punctuated by remissions and exacerbations. The condition can be made worse by exposure to iodides, and this was used as a diagnostic test.

Marks discovered that the disease is associated with a gluten-sensitive enteropathy, identical on jejunal biopsy to that of coeliac disease, but usually without overt symptoms of malabsorption. It is possible to induce a remission of the disease after the exclusion of gluten from the diet for several months. Relapse occurs, however, if gluten is reintroduced. There are granular deposits of IgA in the dermal papillae at the sublamina densa zone of the basement membrane. Antigluten, antigliadin and antireticulin antibodies are present. There is also an IgA endomysial antibody directed against smooth muscle that is found in both dermatitis herpetiformis and coeliac disease and that may reduce with a gluten-free diet. Circulating IgA antibodies are rarely found.

Clinical Features

Symptoms

It is intensely itchy.

Morphology

There are grouped (herpetiform), urticarial papules and vesicles (Fig. 19.53), which are frequently excoriated, because the eruption is so itchy. Healing is associated with postinflammatory hyperpigmentation.

Distribution

The eruption is symmetrical. It affects the areas of skin just below the knees (Fig. 19.54) and elbows (Fig. 19.55), the scalp, scapulae (Fig.

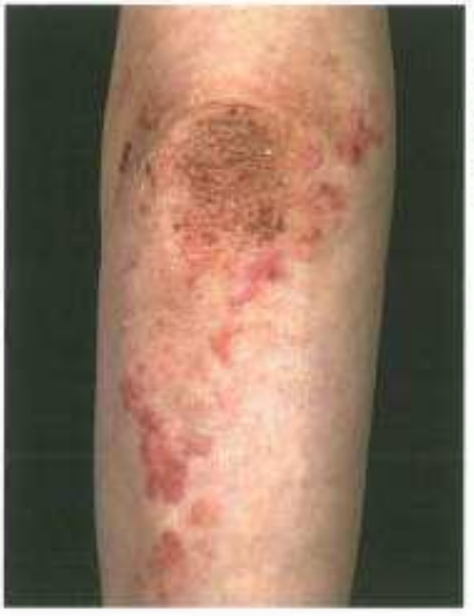


Fig. 19.55 Dermatitis herpetiformis. The skin just below the elbows is involved. The finding of deposits of IgA in the dermal papillae in normal skin confirms the diagnosis.

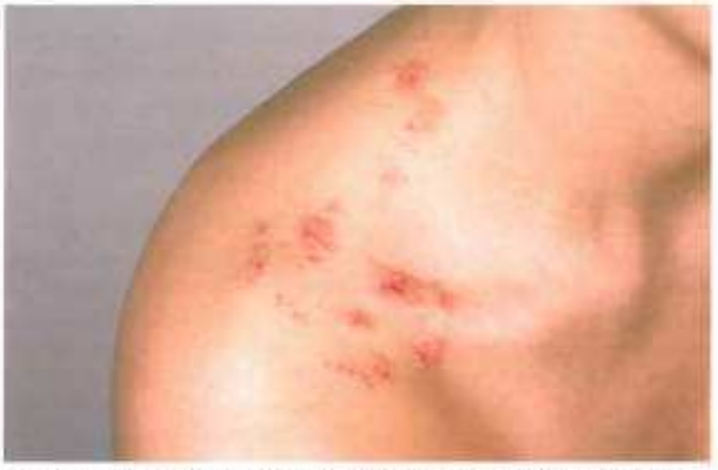


Fig. 19.56 Dermatitis herpetiformis. The front of the shoulders and over the scapulae may be affected. (Courtesy of Dr L. C. Fuller.)

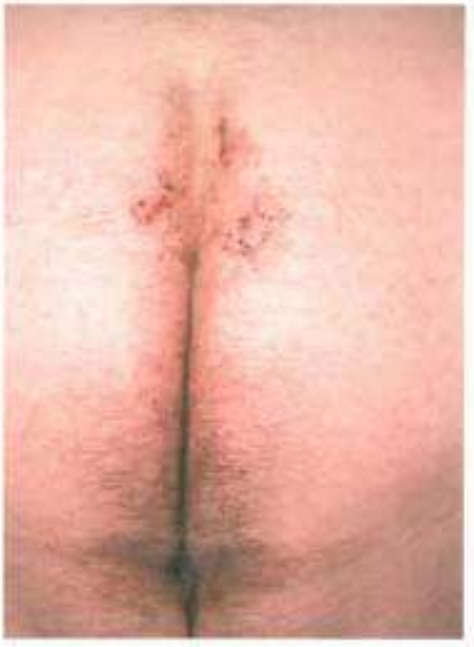


Fig. 19.57 Dermatitis herpetiformis. The lesions are symmetrical and intensely itchy. The buttocks are a characteristic site. It responds rapidly to dapsone and very gradually to a gluten-free diet.

Fig. 19.58 Dermatitis herpetiformis. Neutrophil-rich dermal papillary microabscesses are typical.

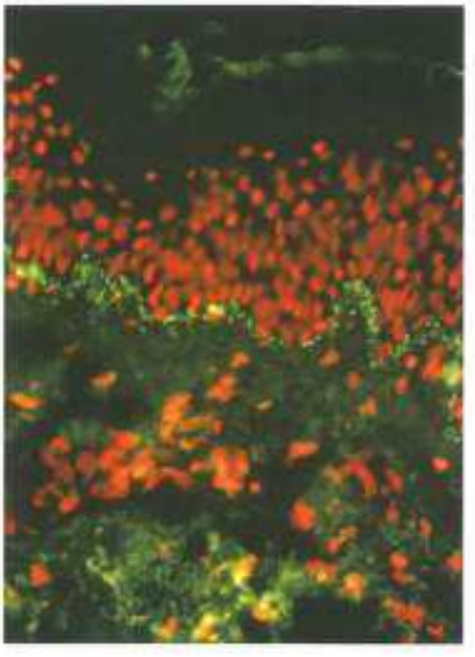


Fig. 19.59 Dermatitis herpetiformis. Granular deposits of IgA in the dermal papillae and along the basement membrane (stained green with immunofluorescence) are pathognomonic of this disease. (Courtesy of Mr B. Bhogal.)

19.56) and buttocks (Fig. 19.57). Occasionally the mucous membranes are involved.

Management

The symmetry and distribution of the eruption, coupled with intense pruritus, usually suggests the diagnosis. Histologically, a neutrophil abscess is found initially in the dermal papillae (Fig. 19.58), followed by a subepidermal multilocular blister with a heavy polymorph infiltrate in the underlying dermis with associated leucocytoclasis. The definitive diagnosis is made by the finding of deposits of IgA (Fig. 19.59) either in perilesional skin or in normal skin (e.g. from the buttocks) at or near the epidermal basement membrane zone.

Overt malabsorption, or indeed any symptom referable to the gastrointestinal tract, is rare, but jejunal biopsy shows changes similar to those described in coeliac disease. Occasionally, patients develop coeliac disease, or vice versa. There is a small risk of gastrointestinal malignancy, in particular lymphoma. A gluten-free diet may protect against this.

The itching ceases within a few hours of taking dapsone 50 mg twice daily but recurs on stopping the drug. If a patient can tolerate a gluten-free diet, the disorder will remit within a few months (sometimes longer) but will recur if the diet is abandoned. The gluten-free diet is unpleasant and many patients compromise with a partial diet and low doses of dapsone. However dapsone may cause haemolytic anaemia and methaemoglobinaemia (Fig. 19.60), particularly in the elderly (and is contraindicated in this group). Alternative drugs are sulphapyridine or sulphasalazine but these also have side-effects. Agranulocytosis and aplastic anaemia do occur very rarely with dapsone. Dapsone is contraindicated in those with glucose 6-phosphate dehydrogenase deficiency. Dapsone does cross the placenta but is not known as a teratogen. It is excreted in breast milk. It very rarely causes a toxic hepatitis and cholestatic jaundice.

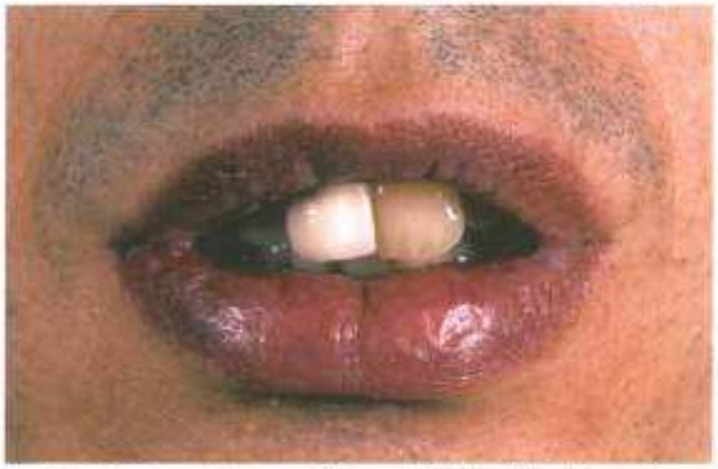


Fig. 19.60 Methaemoglobinaemia. Dapsone is highly effective treatment for dermatitis herpetiformis but may cause methaemoglobinaemia.

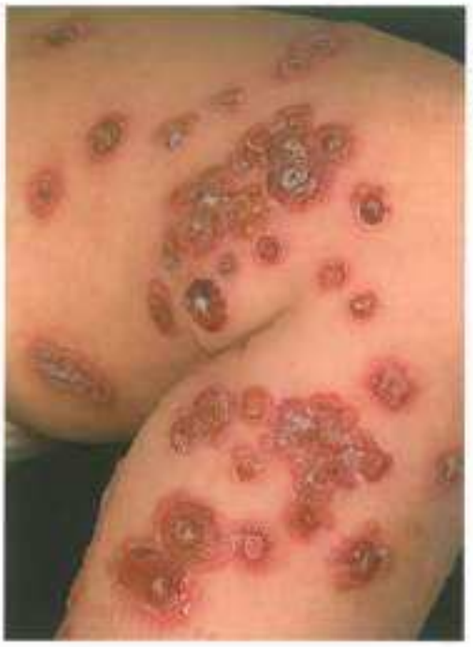


Fig. 19.61 Adult linear IgA disease. The lesions are predominantly bullous. The diagnosis can only be made by immunofluorescence.

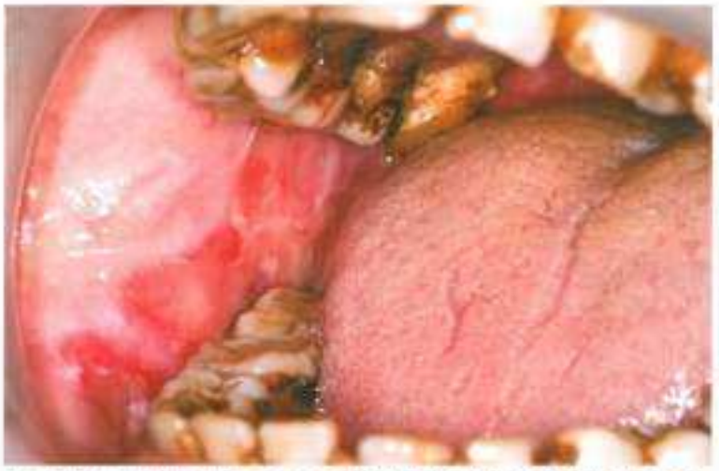


Fig. 19.62 Adult linear IgA disease. Painful ulcers occur on the buccal and the gingival mucosae.

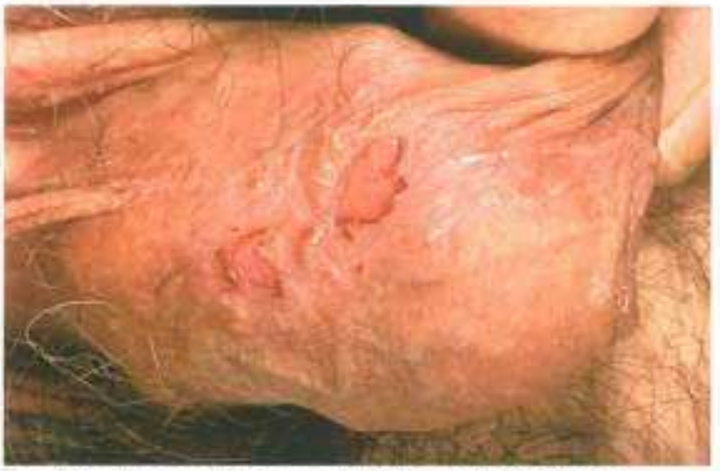


Fig. 19.63 Adult linear IgA disease. Erosions secondary to blisters are present. The eruption is atypical. Immunofluorescence is required for diagnosis.

Adult linear IgA disease

An acquired adult blistering disorder characterized by linear deposits of IgA at the basement membrane zone and circulating IgA antibodies against multiple basement membrane antigens.

Aetiology

The disorder has been separated away from dermatitis herpetiformis because IgA is deposited in a linear manner, which on immunoelectron microscopy is either localized within the lamina lucida or in the sub-lamina densa zone. There is no evidence of small bowel disease and a normal prevalence of HLA-B8 and HLA-DR3 antigens. 30% of patients have circulating IgA antibodies. Other autoimmune disorders may be present.

The target antigens are identical to those in chronic bullous dermatosis of childhood. These include a type 1 97 kDa antigen in the upper lamina lucida and a type 2 290 kDa antigen in the lamina densa and sublamina densa. These appear to be unique to linear IgA disease and chronic bullous dermatosis of childhood, but a number of other target antigens are involved as well.

Vancomycin and diclofenac may cause a *drug-induced linear IgA bullous dermatosis*. There are extensive urticarial, targetoid and bullous lesions on the trunk and limbs, simulating Stevens–Johnson syndrome and toxic epidermal necrolysis.

Clinical Features

There may be itching and burning.

Morphology

The physical signs, although predominantly bullous (Fig. 19.61), are more heterogeneous than in chronic bullous dermatosis of childhood and the disease is often diagnosed as atypical bullous pemphigoid, dermatitis herpetiformis or erythema multiforme until immunofluorescence is performed.

Distribution

The trunk is almost always involved and the limbs, face, scalp, hands and feet usually are. Mucosal involvement is common, both of the mouth (Fig. 19.62), genitalia (Fig. 19.63) and eyes (cicatrizing conjunctivitis).

Management
Immunofluorescence is essential for diagnosis. The condition responds to dapsone, sulphapyridine or sulphasalazine.

Chronic bullous dermatosis of childhood

A chronic autoimmune blistering disorder of young children characterized by linear deposits of IgA at the basement membrane zone.

Aetiology
A linear IgA and C3 pattern similar to that of adult linear IgA disease is found. Circulating IgA antibasement membrane antibodies bind to the epidermal side of salt-split skin and to a 97 kDa target antigen in the upper lamina lucida. Chronic bullous dermatosis of childhood may be distinguished from other blistering disorders that occur in childhood, such as bullous pemphigoid, systemic lupus erythematosus and dermatitis herpetiformis, by the distinct immunoreactant findings.

Clinical Features
Symptoms
The condition may or may not be itchy.

Morphology
Large tense blisters occur, arising from normal or erythematous skin, in groups or annular rosette-like patterns simulating a string of pearls.

Distribution
The blisters can occur anywhere but particularly on the lower trunk including the pelvic regions (Fig. 19.64) and inner thighs.

Management
The diagnosis is made by histology and immunofluorescence and by the finding of circulating IgA antibodies. The course of the disease is punctuated by remissions and exacerbations but the disorder usually disappears completely within 3 years. Treatment is less satisfactory than with other bullous disorders. It may or may not respond to sulphapyridine or sulphones. Sometimes systemic steroids are required in combination with other drugs. The disorder rarely persists into adolescence.

IgA pemphigus

A rare chronic neutrophilic acantholytic autoimmune disease characterized by recurrent subcorneal pustules and IgA deposits on the keratinocyte surface. There are two major subtypes, subcorneal pustular dermatosis and intraepidermal neutrophilic IgA dermatosis.

Aetiology
The two subtypes have a different histopathology and pattern of IgA deposition. In subcorneal pustular dermatosis (also known as *Sneddon–Wilkinson disease*), there is subcorneal acantholysis and pustulosis. The deposits of intercellular IgA are found in the upper epidermis. Desmocollin 1 is the target antigen. In intraepidermal neutrophilic IgA dermatosis, pustules occur deeper in the epidermis and the intercellular IgA is deposited throughout the epidermis. Circulating IgA antibodies are found in 50%. The target antigen is not uniformly characterized, but Dsg1 and Dsg3 are found in some cases. TNF-α may be the principal chemotactic agent because serum levels are raised, and it is found in the blister fluid and some patients respond to anti-TNF-α agents (infliximab and etanercept).

Patients are usually female and over the age of 40, although it can occur at any age. There is no racial preference. Interestingly, the disorder also occurs in dogs. It is responsive to dapsone. Occasionally, it is associated with raised levels of IgA immunoglobulins or an IgA paraproteinaemia, with or without myeloma.

Sneddon–Wilkinson disease has been reported in association with pyoderma gangrenosum, inflammatory bowel disease and rheumatoid arthritis.

Clinical Features
Symptoms
There is an asymptomatic, mainly flexural, rash.

Morphology
It is punctuated by recurrent waves of crops of small, discrete, flaccid vesicles that rapidly become turbid pustules (Fig. 19.65). They may or may not have a transient red erythematous margin. The pustules dry up after a few days and are followed by a superficial scale (Fig. 19.66). The lesions tend to be grouped in an annular or serpiginous manner and postinflammatory hyperpigmentation results.

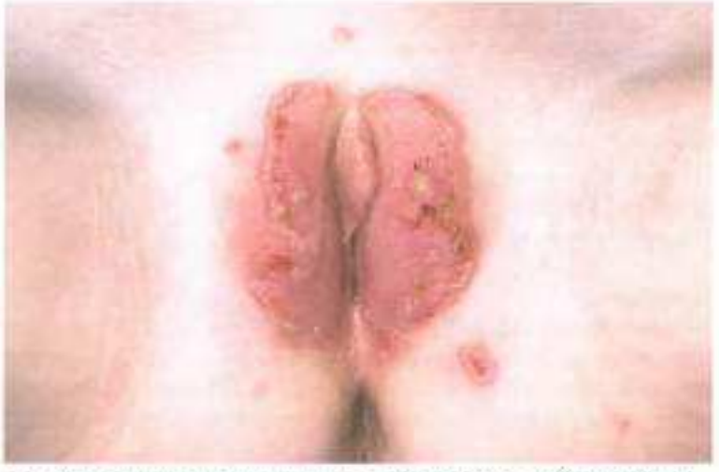


Fig. 19.64 Chronic bullous dermatosis of childhood. Tense blisters occur in an annular manner, often in the genital region. (Courtesy of Dr R. A. Marsden.)

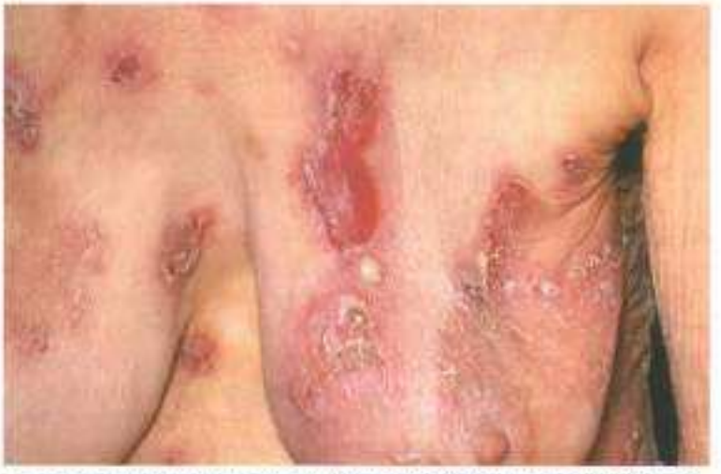


Fig. 19.65 IgA pemphigus. Recurrent waves of turbid pustules occur, which dry and form erosions and superficial crusts, often in the flexures.

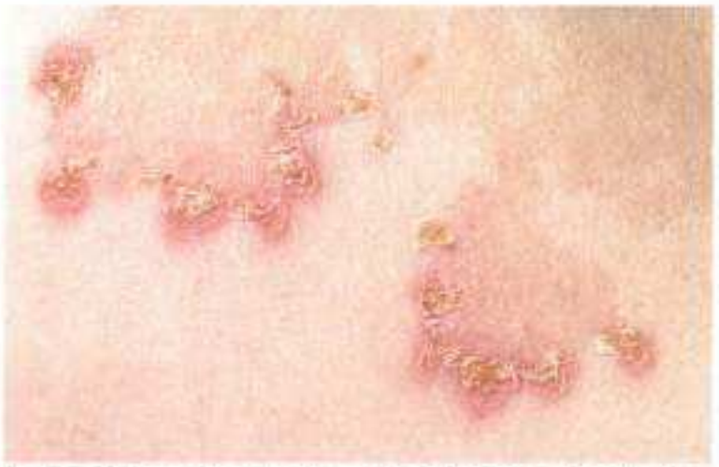


Fig. 19.66 Subcorneal pustular dermatosis. The lesions may be annular. Very superficial flaccid blisters are visible at the edge, with scaling and crusting and postinflammatory pigmentation.

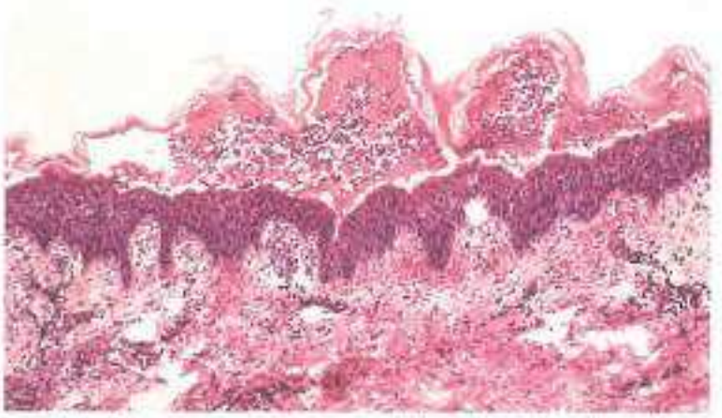


Fig. 19.67 Subcorneal pustular dermatosis. Immediately below the stratum corneum is a vesicle containing many neutrophil polymorphs.

Distribution

The eruption is symmetrical and recurs in the flexures (the axillae, under the breasts and in the groin), abdomen or the flexor surfaces of the limbs. The mucous membranes are not affected.

Management

Histologically there is a perivascular infiltrate with neutrophils and occasionally eosinophils. The neutrophils migrate through the epidermis and collect beneath the stratum corneum on the surface of the epithelium (Fig. 19.67).

Sneddon–Wilkinson disease responds to dapsone, albeit more slowly than dermatitis herpetiformis. Potent topical steroids, systemic steroids, acitretin and psoralen–ultraviolet A (PUVA) therapy have all been tried. Chemotherapy, for any associated gammopathy, can improve the clinical features. The differential diagnosis is from impetigo, where bacterial swabs are positive, and pustular psoriasis, which does not respond to dapsone.

Developmental disorders of the skin 20

Ichthyosis

The term 'ichthyosis' (Greek, fish) refers to a scaly appearance of the skin. It includes a group of disorders that present either at birth or in early childhood. They are characterized by a chronic, generalized and – in the common varieties – non-inflammatory scaling of the skin. The fundamental defect is a failure to shed (desquamate) the corneocytes (the cells of the stratum corneum) properly.

The corneocytes are built of proteins and connect to each other with a lipid material. Cornification begins in the suprabasal layer in postmitotic keratinocytes with the synthesis of precursor proteins and lipids. The cells become cuboidal through the spinous and granular layers and flatten, enlarge, lose organelles and become dehydrated in the cornified layer. Corneocytes are filled with bundles of keratin filaments, which are assembled by filaggrin (a histidine-rich interfilamentous protein derived from profilaggrin, which is the major protein of keratohyalin granules). This process is carefully regulated by proteolysis and dephosphorylation, which generate the requisite free amino acids to contribute to the water-holding properties of the stratum corneum. The rigid, cornified envelope is produced by cross-linking of precursor proteins (for example involucrin and loricin), catalysed by transglutaminases. Individual corneocytes interdigitate and are further bound by corneodesmosomes, which disintegrate during the transition from the inner to the outer stratum corneum. Lamellar (Odland) bodies are small ovoid organelles that are synthesized within the spinous and granular cells and contain glycosphingolipids, phospholipids and cholesterol. They secrete their contents into the intercellular domain and are responsible for the lipid-rich bilayered intercellular membrane system. The conversion of cholesterol by cholesterol sulphatase on the cell membrane surface leads to the breakdown of this intercellular lipid lamella and results in desquamation. Failure of this intercellular lipid lamella leads to increased transepidermal water loss, which is a characteristic feature of ichthyosis.

Ichthyosis may be inherited or acquired. Acquired causes are:

- malignancy, e.g. lymphoma, myeloma and Kaposi's sarcoma
- autoimmune, e.g. systemic lupus erythematosus, dermatomyositis, sarcoidosis and graft-versus-host disease
- metabolic, e.g. chronic renal or liver failure, hypothyroidism, hypopituitarism and hyperparathyroidism
- nutritional, e.g. essential fatty acid deficiency, malabsorption (coeliac and pancreatic insufficiency) and malnutrition
- infection, e.g. AIDS, HTLV1 and 2, and leprosy
- drugs, e.g. cimetidine, clofazamine, hydroxyurea, cholesterol-lowering agents, nicotinic acid and triparanol.

Inherited causes include:

- Inborn errors of metabolism such as Refsum's disease, X-linked ichthyosis vulgaris, neutral lipid storage disease and Sjögren–Larsson syndrome.

Refsum's disease is a rare, autosomal recessive, neurocutaneous disorder that results from failure to catabolize phytanic acid, a fatty acid found in green vegetables. The phytanic acid accumulates and displaces unsaturated fatty acids, such as linoleic acid, from tissue lipids. There is ichthyosis, particularly on the lower trunk and limbs, which resembles ichthyosis vulgaris clinically and histologically, but ultrastructurally lipid droplets are found in the basal and suprabasal layers. The neurological signs may be delayed until adolescence or the early twenties but then the disease is progressive with cerebellar ataxia, peripheral neuropathy (with hypertrophied peripheral nerves) and retinitis pigmentosa. Neural deafness, anosmia, skeletal abnormalities and pupillary dysfunction also occur. It is caused by mutations in the *PHYH* (*PAHX*) or *PEX7* genes leading to deficiency of the perioxisomal enzyme phytanoyl-CoA hydroxylase. Treatment is severe restriction of dietary phytanic acid.

Neutral lipid storage disease (*Chanarin–Dorfman syndrome*) is an autosomal recessive, multisystem lipoidosis with the accumulation of neutral lipids (triglycerides) in white blood cells (polymorphs and monocytes), skin, liver, muscles and eyes (producing cataracts in half the patients). It occurs particularly in consanguinous marriages in those of Mediterranean or Arabic descent. Cutaneous clinical features are varied. The infant may be born erythrodermic or encased in a collodion-like membrane and progress to a mild-to-moderate, non-bullous, ichthyosiform, erythrodermic pattern, with fine, white scaling on an erythematous background with lamellar scales on the legs. Pruritus is troublesome and there is hyperhidrosis, mild ectropion, flexural lichenification, palmar-plantar hyperkeratosis and nail dystrophy. There is hepatomegaly, occasionally splenomegaly and malabsorption (from intestinal mucosal lipid deposition), nerve deafness, neuropathy and, in some patients, intellectual impairment, microcephaly and short stature. The diagnosis may be made by finding vacuoles in the leucocytes that stain positively with Sudan Black but the histology of the skin is also useful. There is acanthosis and hyperkeratosis and closely packed lipid droplets are found in the basal, granular and adnexal keratinocytes. It is caused by a mutation in the *ABHD5* gene on chromosome 3p21.33.

The *Sjögren–Larsson syndrome* is an autosomal recessive disorder of congenital ichthyosis, spastic diplegia and mild-to-moderate mental retardation. There are reduced levels of hexanol dehydrogenase in the skin and the gene for this enzyme is carried on chromosome 17 not far from the gene linked to neurofibromatosis. There is occasionally a collodion covering at birth but usually the skin is dry and mildly erythrodermic. There is a variable degree of scaling, which leads to light peeling of the trunk with more lamella-like lesions on the legs. There is a cyclical pattern of accumulation and shedding of the skin. There is a velvety orange or brown lichenification, with verrucose hyperkeratosis of the flexures, neck and periumbilical folds. The neurological abnormalities are usually obvious from early infancy. There are delayed motor milestones and upper motor neurone weakness affecting the legs but rarely the arms. There are glistening dots to be found on the fovea of the retina. The condition is rarely seen outside Sweden where it may be traced back to a common ancestry. The disorder was described by two psychiatrists following examination of some of their patients in a mental institution. The diagnosis may be confirmed by measuring fibroblast fatty aldehyde dehydrogenase, which is reduced.

Dysfunction of organelles such as lamellar bodies and peroxisomes occur in Conradi's syndrome, CHILD syndrome, the harlequin fetus and congenital ichthyosiform erythroderma.

Conradi's syndrome is an erythroderma with scales that occur in a characteristic whorled pattern. These are subsequently replaced by follicular atrophy. There is also a shortening of the humerus and femur, lens opacities and a high, arched palate; stippling of the epiphyses can be seen

on radiographs. The Conradi–Hünermann syndrome, the CHILD syndrome and rhizomelic chondrodysplasia punctata have in common limb reduction defects; chondrodysplasia punctata and ichthyosis and peroxisomal deficiency may underline these abnormalities. Peroxisomes are multifunctional organelles involved in various oxidative and biosynthetic pathways including those of lipid metabolism.

The *CHILD syndrome* is a rare unilateral inflammatory epidermal naevus or ichthyosiform erythroderma involving Blaschko's lines and associated with skeletal abnormalities. The acronym refers to congenital hemidysplasia with ichthyosiform erythroderma or naevus and unilateral limb defects.

The more common inherited disorders of ichthyosis vulgaris, X-linked ichthyosis and the ichthyosiform erythrodermas are described more fully here.

ICHTHYOSIS VULGARIS

A common, autosomal dominant inherited disorder that results in widespread dryness and scaling of the skin.

Aetiology

The incidence is estimated at 1 in 250, but the manifestations vary greatly. The discoveries of the loss of the granular cell layer on light microscopy and of profilaggrin keratohyaline granules on electronmicroscopy led to the finding of loss of function mutations in filaggrin genes. Filaggrin is a filament aggregating protein, which is necessary for the formation of the stratum corneum. There is therefore impaired keratinization and adherence of corneocytes and consequent scaling. Lack of water containing amino acids, which are produced when filaggrin is catabolized result in the perceived dryness. There is often associated atopic eczema. The condition is worse in winter and improves in summer, sometimes virtually clearing in warm humid climates. It may improve in adult life but deteriorates once again in old age.

Clinical Features

Symptoms

The entire skin becomes dry and rough (Fig. 20.1) in infancy or early childhood.

Morphology

There are small, fine, white scales. Larger, more adherent, scales are seen on the fronts of the shins.

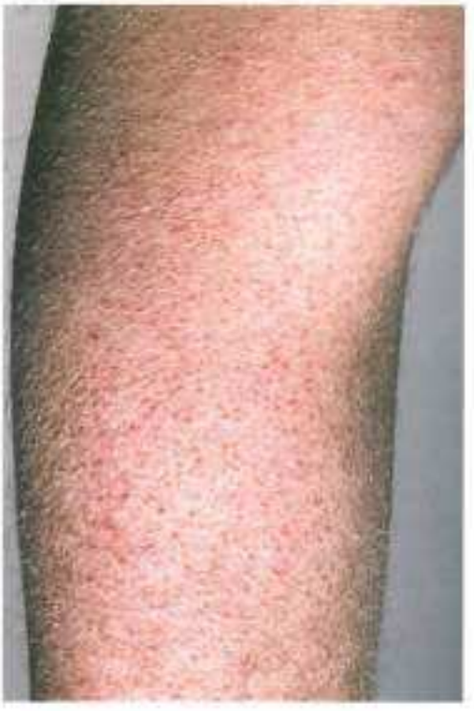


Fig. 20.1 Ichthyosis vulgaris. The skin feels dry and rough. The skin creases are prominent and there may be fine scaling.

Distribution

Extensor surfaces of the limbs and on the trunk with a characteristic sparing of the flexures, especially of the knees (Fig. 20.2) and elbows. The forehead, cheeks and scalp may be involved. In some individuals, the follicular orifices on the upper outer arms and thighs are plugged with keratin (Fig. 20.3), which forms spines (keratosis pilaris). The palmar and plantar skin creases are often exaggerated (Fig. 20.4) and frequently there is hyperkeratosis. Fissuring of the fingertips in cold weather is characteristic.

Diagnosis

Biopsy shows that the epidermis and stratum corneum are of normal thickness but the granular cell layer is absent (Fig. 20.5), which distinguishes ichthyosis vulgaris from other forms. The hyperkeratosis is not marked.

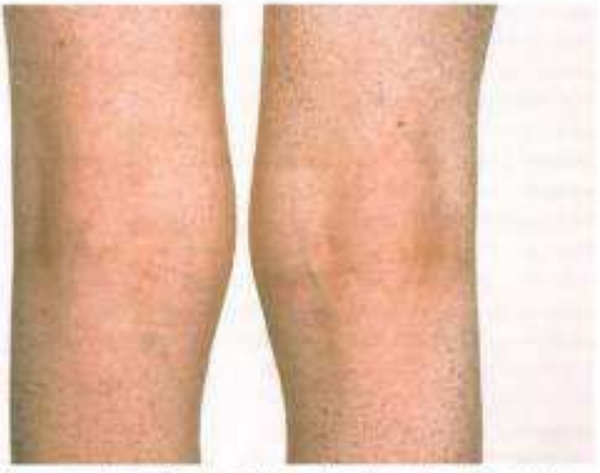


Fig. 20.2 Ichthyosis vulgaris. The skin is dry and rough, and very fine scales may be seen. The flexures, e.g. the backs of knees here, are characteristically spared.

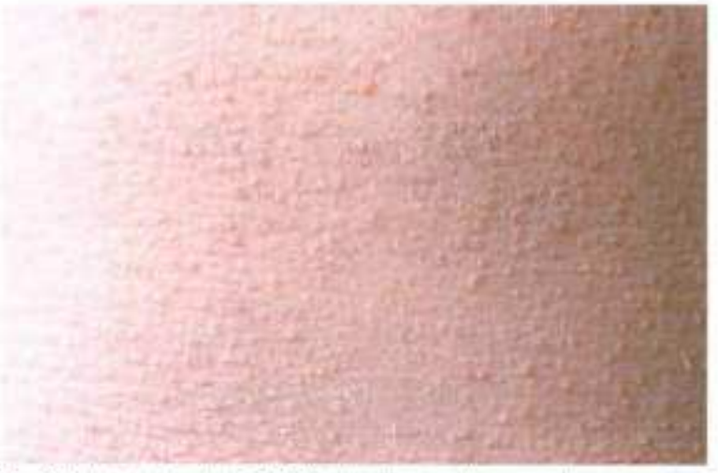


Fig. 20.3 Keratosis pilaris. The follicular orifices on the upper outer arms and thighs are plugged with keratin. This frequently accompanies ichthyosis vulgaris.

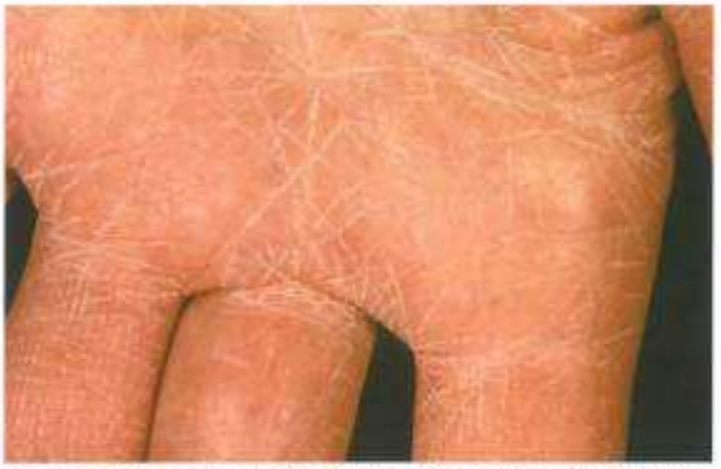


Fig. 20.4 Ichthyosis vulgaris. The palms and soles may be involved. The skin is dry and rough, especially in the creases. Cracking of the skin occurs in the cold.

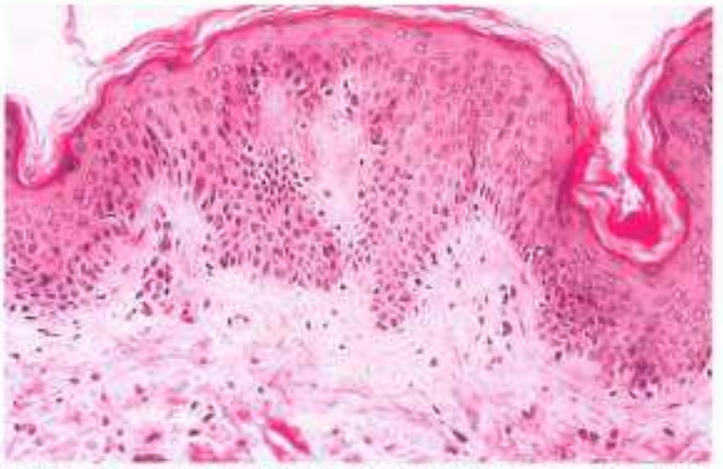


Fig. 20.5 Ichthyosis vulgaris. The changes of hyperkeratosis associated with an absent granular cell layer are subtle and easily overlooked.

X-LINKED ICHTHYOSIS VULGARIS

An uncommon recessive disorder that occurs in males due to steroid sulphatase deficiency resulting in large, dark scales over the entire skin.

Aetiology

Steroid sulphatase deficiency results from deletions in the steroid sulphate (*STS*) gene on Xp22 and females are therefore asymptomatic carriers. The mothers of these patients have low urinary oestrogens in pregnancy. These are required for proper ripening of the cervix, and deficiency leads to prolonged labour, which often necessitates a Caesarean section. Maternal urinary oestrogens are derived from dehydroepiandrosterone sulphate, which is secreted by the fetal adrenal cortex. This is desulphated to dehydroepiandrosterone in the placenta by the enzyme steroid sulphatase. Patients with sex-linked recessive ichthyosis lack steroid sulphatase in the skin, stratum corneum, hair follicles, leucocytes, fibroblasts, amniotic fluid cells and placenta. The abnormality results from the accumulation of the substrate cholesterol sulphate between the cells of the stratum corneum, which impedes desquamation. In addition to the obstetric and perinatal complications, there are extracutaneous abnormalities. There is cryptorchidism, abnormalities of spermatozoa leading to infertility, and increased risk of teratoma. There may be inguinal hernia and unilateral renal agenesis. There are corneal opacities in affected males and in female carriers that do not affect vision, but which may be seen on slit lamp examination.

Kallman's syndrome is X-linked recessive ichthyosis associated with hypogonadotrophic hypogonadism, anosmia and neurological abnormalities of nystagmus and mirror movements of the hands and feet. It results from a contiguous gene defect proximal to and including the steroid sulphatase gene. There may be associated obesity, osteoporosis, cleft palate, developmental delay and spastic paraplegia.

Clinical Features

Symptoms

It presents within the first year. The skin is dry and looks dirty.

Morphology

There are large, dark scales (Fig. 20.6).

Distribution

All the skin is involved (Fig. 20.7), in particular the extensor surfaces and including the ears, neck and scalp. The hair may be coarse and dry. The

Fig. 20.6 X-linked ichthyosis vulgaris. The individual scales are coarser, larger and darker than those of ichthyosis vulgaris.

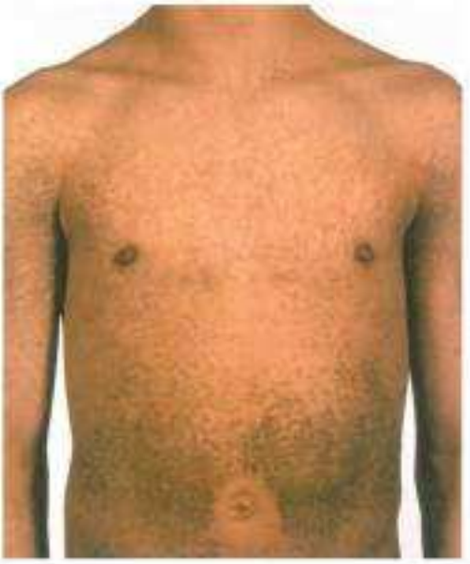


Fig. 20.7 X-linked ichthyosis. The condition involves all the skin, particularly the extensor surfaces. Unlike ichthyosis vulgaris, dark, polygonal scales are present, the palms/soles are normal and there is no association with keratosis pilaris or atopy.

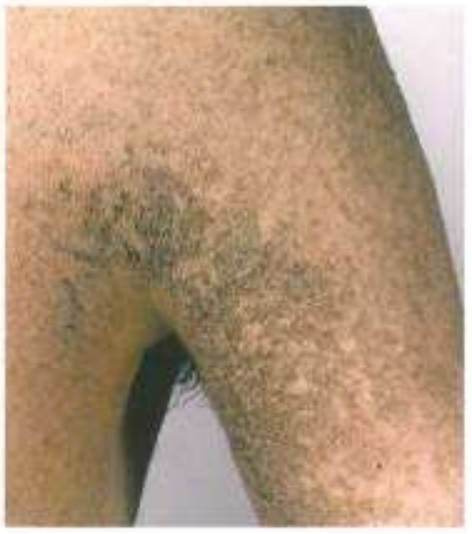


Fig. 20.8 X-linked ichthyosis. It is confined to males and does not improve with age. It gives a false impression of dirt. It is due to steroid sulphatase deficiency.

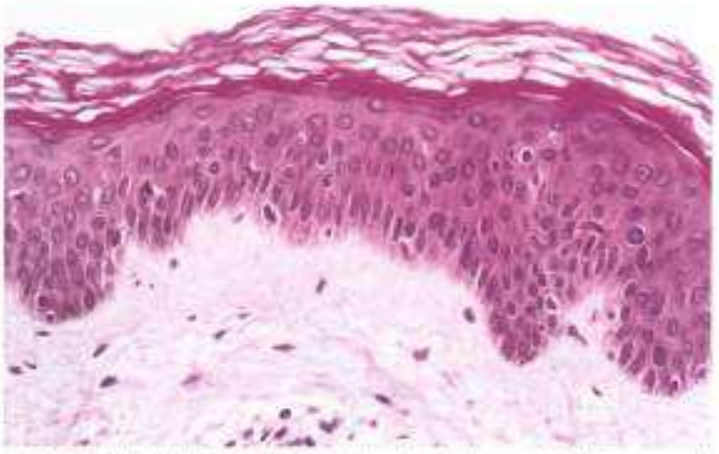


Fig. 20.9 X-linked ichthyosis. There is hyperkeratosis associated with a normal granular cell layer (unlike ichthyosis vulgaris). The epithelium is sometimes acanthotic.

condition may be distinguished from ichthyosis vulgaris because of the large dark scales (Fig. 20.8), involvement of the flexures and normal palms and soles. Keratosis pilaris is not present and there is no association with atopy.

The condition is lifelong and does not improve with age, although it does improve in warm, humid weather.

Histopathology

The granular cell layer is normal (unlike ichthyosis vulgaris). There is hyperkeratosis, a slightly acanthotic epidermis (Fig. 20.9) and a lymphocytic perivascular inflammatory cell infiltrate.

Diagnosis

Cholesterol sulphate and steroid sulphatase can be measured in fibroblasts, white cells, whole skin or scale. Cholesterol sulphate is also carried on low density lipoprotein particles in the serum and makes them more electronegative; consequently, in standard lipoprotein electrophoresis, these particles will migrate more rapidly towards the positive pole, which makes the diagnosis simple. Fluorescent in situ hybridization (FISH) permits rapid screening for the microdeletion on the X-chromosome. Prenatally, steroid sulphatase may be measured in cultured cells.

LAMELLAR ICHTHYOSIS AND CONGENITAL NON-BULLOUS ICHTHYOSIFORM ERYTHRODERMA

These are autosomal recessive disorders of cornification that are characterized clinically by excessive scaling and histologically by epidermal hyperplasia and increased epidermal turnover.

Aetiology

The terms non-bullous ichthyosiform erythroderma (Fig. 20.10) and lamellar ichthyosis have been used synonymously, but there is increasing evidence that they are distinguishable clinically, histologically, biochemically and genetically. Both are autosomal recessive diseases and there is a high instance of consanguinity. They constitute a spectrum with intermediate phenotypes ranging from the rarer lamellar ichthyosis, where there are large dark plate-like scales and little or no erythroderma to congenital non-bullous ichthyosiform erythroderma, where there is a generalized redness and fine, white scales with little or no ectropion, eclabium or alopecia. Not all patients fit neatly into these two distinctions. There are at least four different genetic loci (genetic heterogeneity) but producing identical clinical phenotypes. *TGM1* on chromosome 14q21, *ABCA12* (ATP-binding cassette), a transporter gene on chromosome 2q35, *ALOXE3* and *12B* on 17p13.1 and ichthyin on 5q33.3 and 19p13.1-2. Transglutaminase-1 (*TGM-1*) catalyses the Ca^{2+}-dependent cross-linking of proteins in the upper differentiated layers of the epidermis. Deficiency of *TGM-1* disturbs cornification. A very rare and most distinct form of *ABCA12* mutation is the *Harlequin fetus*. It is a life-threatening form of ichthyosis in which there is an armour of very thick plates of stratum corneum separated by fissures. The ears are absent or rudimentary. There is gross ectropion and marked eclabium, presenting a horrific appearance. Some have responded to the lipid-raising effects of retinoids.

Clinical Features

Symptoms

The child is almost always born with a collodion membrane.

Morphology

In lamellar ichthyosis, the infant is born encased in a collodion membrane and may be red at birth, although this disappears. There is tautness of the facial skin that leads to traction on the eyelids and lips and, thus,

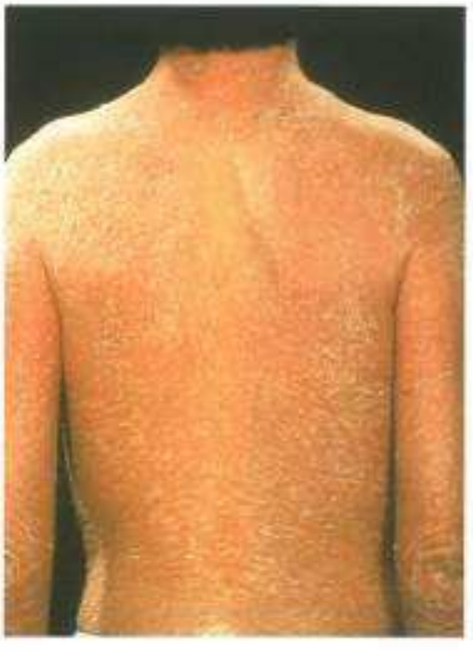


Fig. 20.10 Non-bullous ichthyosiform erythroderma. There is erythroderma and diffuse white scaling. (Courtesy of Dr John Harper.)

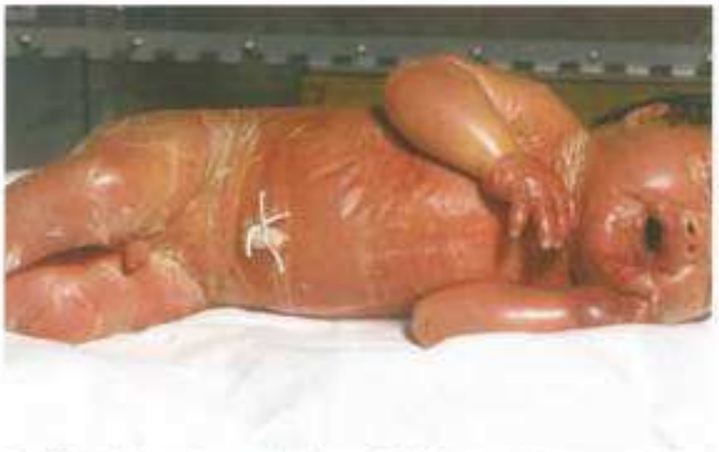


Fig. 20.11 Ichthyosiform erythroderma. The infant may be born encased in a collodion-like membrane, which may also occur in lamellar ichthyosis, neutral lipid storage disease, Sjögren–Larsson syndrome and self-healing collodion baby.

Fig. 20.12 Non-bullous ichthyosiform erythroderma. This patient had fine white scaling in contrast to the dense plate-like scales of lamellar ichthyosis.

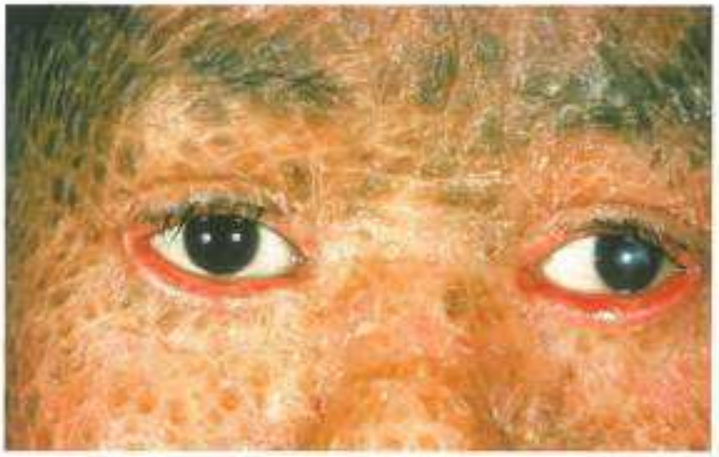


Fig. 20.13 Lamellar ichthyosis. Ectropion is usually prominent. Dense plate-like scales are characteristic. (Courtesy of St Mary's Hospital.)

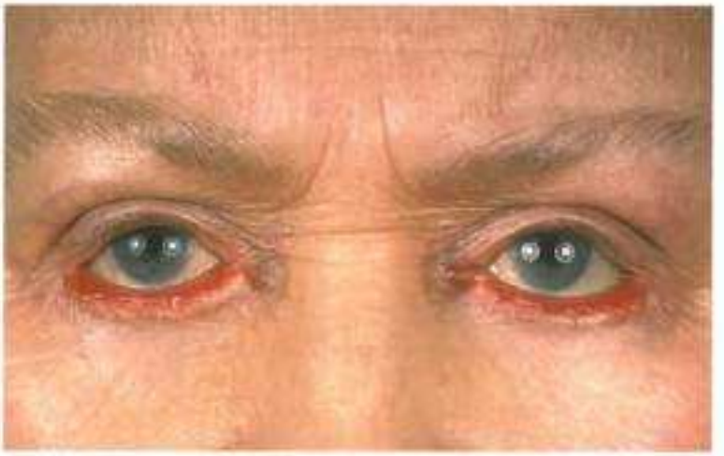


Fig. 20.14 Non-bullous ichthyosiform erythroderma. This patient had ectropion, fine white scaling and did not sweat in warm weather.

to ectropion and eclabion. There may be a scarring alopecia secondary to the encasement of the hair by the thick stratum corneum, particularly at the peripheries of the scalp. The palms are variably involved, ranging from minimal hyperlinearity to severe keratoderma.

In congenital ichthyosiform erythroderma, the infant may be born encased in collodion (Fig. 20.11) but subsequently there is a generalized erythema and fine, white scales (Fig. 20.12), although the scales may be larger and darker on the lower leg and hyperkeratotic on the palms and soles, which improve at puberty. Those affected may have minimal sweating and, therefore, heat intolerance. The nails may be ridged.

Distribution

Although all the skin is involved, the condition gradually becomes verrucous around the joints. The hands and feet may be severely fissured, which makes them difficult to use. The scalp hair may be bound up in scale, and scarring alopecia may result from frequent sepsis. The nails are abnormal with ridges and grooves. Ectropion is an important diagnostic sign (Figs 20.13 and 20.14). The mucous membranes are spared.

Systemic features

These patients do not sweat because of obstruction of the glands, and hyperpyrexia may be a problem in warm weather or during exercise. Complications associated with the disorder are frequent skin infections and, in infancy, there may also be a failure to thrive because of loss of protein in the scale.

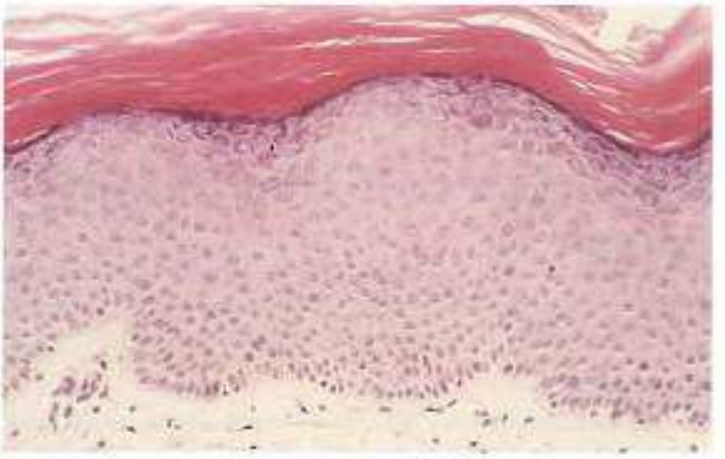


Fig. 20.15 Lamellar ichthyosis. There is hyperkeratosis, acanthosis and an increased granular cell layer.

Diagnosis

Histologically, there is a variable degree of epidermal hyperplasia and hyperkeratosis (Fig. 20.15). Immunostaining shows absence of KRT1 or 10 and DNA-based molecular staining for TGM-1 and ABCA-12 should assist diagnosis. These can also be performed prenatally.

CONGENITAL BULLOUS ICHTHYOSIFORM ERYTHRODERMA OF BROCQ

An autosomal dominant epidermolytic condition caused by mutations in keratin 1 and 10 genes resulting in generalized erythema, scaling and blistering.

Aetiology

Although inherited as an autosomal dominant, 50% are sporadic. There are at least six clinical phenotypes resulting from heterozygous mutations in *KRT1* on 12q13.3 (with severe involvement of the palms and soles) and *KRT10* on 17q21.2, expressed in the suprabasal and granular cell layers. The cytoskeleton is weakened, leading to cytolysis, blistering and disturbance of barrier function. Transepidermal water loss and malodorous skin sepsis are major problems.

Lamellar body secretion is abnormal because of mutations in the genes encoding for keratin 1 and 10, which are expressed in suprabasal keratinocytes. They alter keratin filament structure and, therefore, filament–desmosomal connections; this leads to mechanical fragility and blistering in the neonate and to hyperplasia and scaling later as more lamellar bodies are made with the change from a wet to an arid environment after birth. On electron microscopy, clumping of filaments are seen to begin in the first suprabasal layer.

It is usually generalized (Fig. 20.16), but it may present in a localized manner as a linear epidermolytic epidermal naevus, and parents have been described as having offspring with bullous ichthyosiform erythroderma. A mutation in the basal cells (keratins 1 and 10) probably occurs late enough after fertilization to affect some of the epidermal cells along the lines of Blaschko but early enough to be in the cells that contribute to the gonads.

There is a variation of the disorder that is localized to the palms and soles and is caused by an abnormality of keratin 9 (Voerner type). BCIE is a heterogeneous disease and has now been divided into various subtypes, particularly dependent on whether palmar-plantar hyperkeratosis is present or absent and also based on the presence or absence of erythroderma, the extent of involvement, the presence of digital contractures and the quality of the scale. This may be massive and verrucous in some cases, producing firm, porcupine-like hyperkeratotic spines (ichthyosis hystrix) often arranged linearly in the flexural creases. Skin infections are frequent and patients often emit a pungent odour. Ichthyosis hystrix is a descriptive term for a clinical and genetic heterogeneous group of skin disorders, which may result from BCIE.

Clinical Features

Symptoms

Blistering occurs particularly at sites of trauma at or shortly after birth.

Morphology

The blisters and erosions (Figs 20.17 and 20.18) gradually resolve although they may recur periodically in adult life. There is general erythema and scaling (Fig. 20.19), which also usually becomes less prominent.

Distribution

The whole cutaneous surface is involved but gradually keratotic or even verrucous (Fig. 20.20) lesions become pronounced around the flexures (Fig. 20.21).

The hair and mucous membranes are quite normal. Bacterial infection is common and serious, and often distressingly malodorous. Alopecia may result from scalp sepsis.

Diagnosis

The histology is characteristic, with giant coarse keratohyalin granules and vacuolation of the granular layer with lysis of the suprabasal keratinocytes (Fig. 20.22) (hence its synonym *epidermolytic hyperkeratosis*).

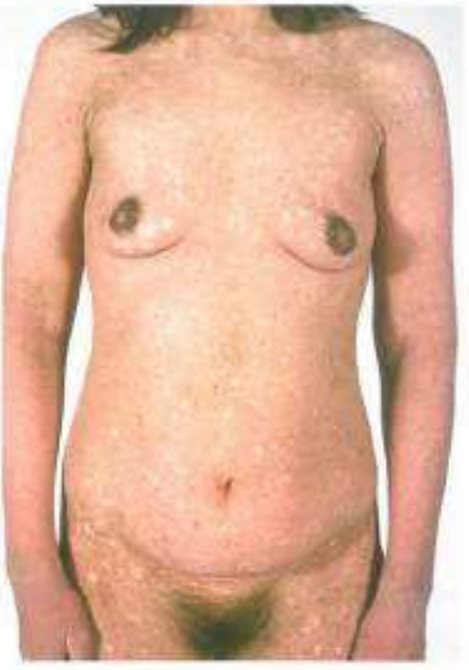


Fig. 20.16 Bullous ichthyosiform erythroderma. There is erythema and flexural verrucous scaling, which persists throughout life. Previous blisters have resulted in scarring. (Courtesy of St Mary's Hospital.)

The cell membranes may break up to form subcorneal, multiloculated blisters. There is acanthosis, papillomatosis and a basket weave-like pattern to the thickened stratum corneum. Electron microscopy shows loss of the normal pattern of tonofilaments and a decrease in desmosomal contacts. These findings are useful for making the diagnosis prenatally by fetoscopy and skin biopsy.

A milder form is *ichthyosis bullosa of Siemens*. There are mutations of the keratin 2e (K2e) gene expressed suprabasally, mainly in the granular cell layer. Clinically, there are trauma-induced blisters, which improve with age, associated with a rippled hyperkeratosis of the skin overlying the joints (often mistaken for eczema) and dorsa of the palms and soles. There is general scaling and dryness with localized areas of peeling known as 'mauserung'.

Management of Ichthyosis and Related Disorders

The pliability and suppleness of the stratum corneum improves if its water content is increased. Occlusive materials that prevent the evaporation of water, such as petrolatum, are the mainstay of treatment. Other available greasy materials include true fats, waxes, mineral greases and macrogols.

Emulsions are commonly used in dermatology. These are a dispersion of two or more immiscible liquid phases, usually aqueous and oily, which are thermodynamically unstable and which tend to separate out. Emulsifying agents, such as sodium lauryl sulphate, are added to improve stability by reducing surface tension. Thus, aqueous cream is an example of an oil/water system where oil is dispersed as small droplets in water; it consists of 30% emulsifying ointment and 70% water with chlorocresol as a preservative. Emulsifying ointment itself is 30% emulsifying wax (which contains sodium lauryl sulphate), 20% liquid paraffin and 50% white soft paraffin.

Such emollients can be used as moisturizers or soap substitutes and bath additives. Commonly used emollients are:

- **Moisturizers** Examples are aqueous cream, E45 cream and Aquaphor (popular in the USA, related to woolfat).
- **Soap substitutes and bath additives** Examples include emulsifying ointment and various preparations based on liquid paraffin. Bath additives based on a colloidal oat fraction or on soya oil are also favourites.
- **Urea-containing preparations** Creams contain 10% urea.
- **Lactic acid preparations** Emollients contain lactic acid.

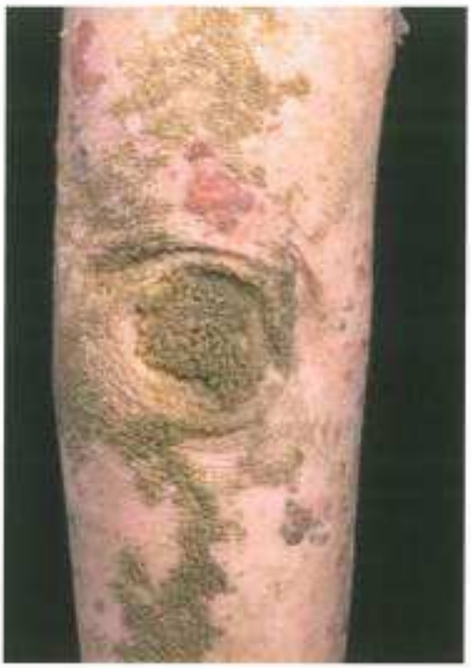


Fig. 20.17 Bullous ichthyosiform erythroderma. Blisters are followed by erosions and linear hyperkeratosis. (Courtesy of Dr John Harper.)

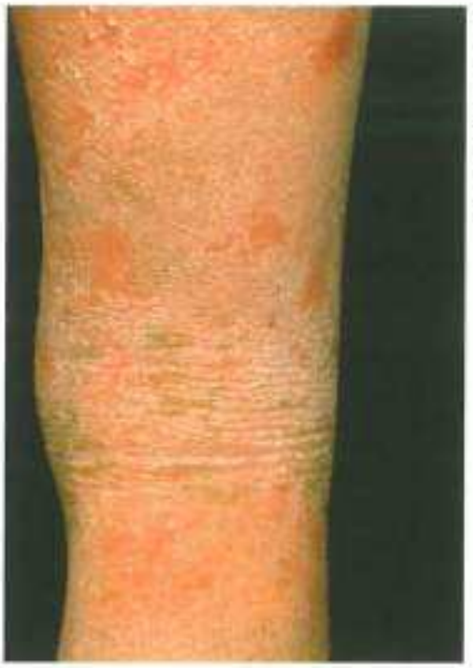


Fig. 20.18 Bullous ichthyosiform erythroderma. Erosions and hyperkeratosis are present. The erythroderma has disappeared. (Courtesy of the Institute of Dermatology.)

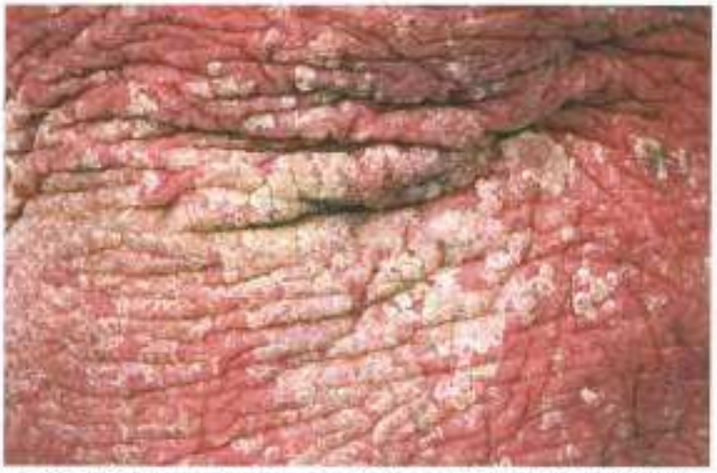


Fig. 20.19 Bullous ichthyosiform erythroderma. The erythroderma and warty scaling is clearly illustrated here.

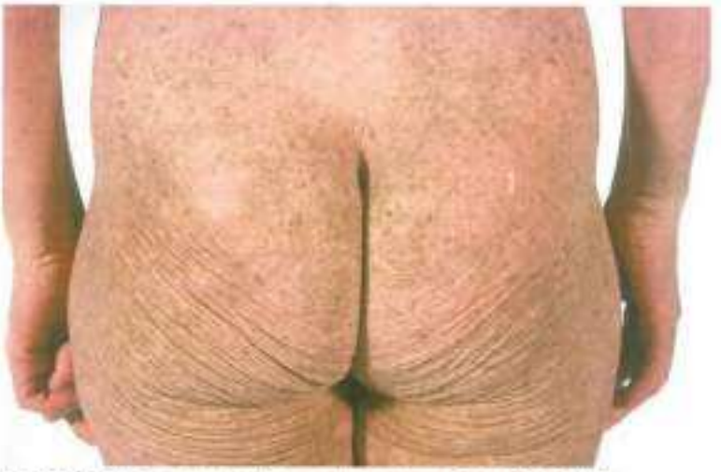


Fig. 20.20 Bullous ichthyosiform erythroderma. The scaling is thick, almost verrucous, and is most prominent around the flexures. (Courtesy of St Mary's Hospital.)

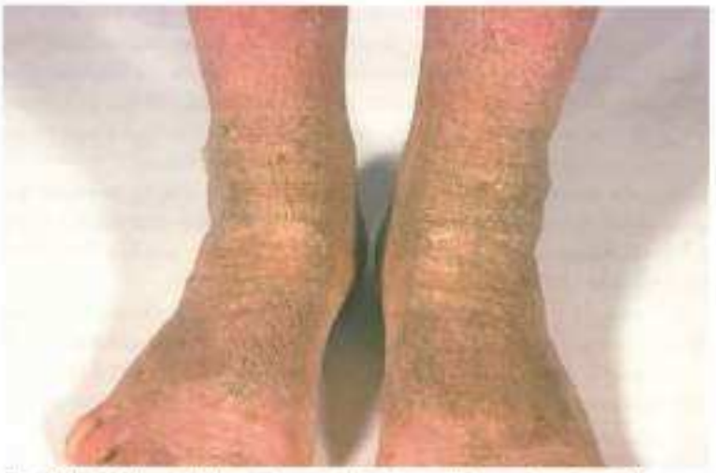


Fig. 20.21 Bullous ichthyosiform erythroderma. The warty scaling and fissuring is particularly marked around the flexures. (Courtesy of St Mary's Hospital.)

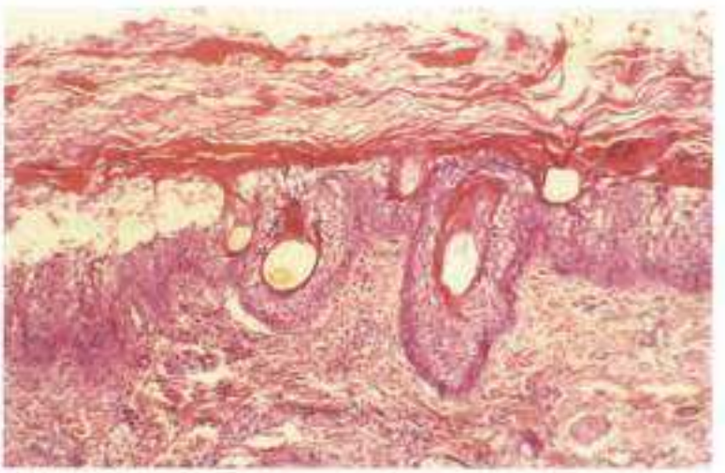


Fig. 20.22 Bullous ichthyosiform erythroderma. There is massive hyperkeratosis, vacuolation of the granular cell layer and lysis of the suprabasal keratinocytes.

- **Menthol (1%) and phenol (2%) in aqueous cream** This is particularly helpful for winter itch.

In general, it is important to emphasize the deleterious effect of excess bathing and washing on dry skin, especially in winter.

Retinoids, such as etretinate and its derivative acitretin, are a major advance in the treatment of serious forms of ichthyosis. Non-bullous ichthyosiform erythroderma, lamellar ichthyosis and sex-linked ichthyosis are improved. The effects in bullous ichthyosiform erythroderma are less dramatic because patients are prone to increased skin fragility induced by the retinoid. Netherton's syndrome (see below) is made worse. Retinoids are not indicated for the common forms of ichthyosis as long-term side-effects are not yet known. The drugs increase lipid levels, are teratogenic and potentially hepatotoxic. In studies with large doses, premature closure of the epiphyses, osteoporosis, periosteal thickening, hyperostoses and ligamentous calcification have been described.

It is important to note that ichthyotic and xerotic conditions do not respond to topical steroids, except when eczema is present, in which case class III (potent) steroids are invaluable, for example in the treatment of winter itch. The choice of vehicle is important: ointments are most helpful and creams are best avoided since they exacerbate dryness.

Netherton's syndrome

A rare autosomal recessive disorder of cornification characterized by a triad of congenital ichthyosiform erythroderma, hair shaft defects and immunodeficiency.

Aetiology

There is a defect in the *SPINK5* gene on chromosome 5q33.1, which encodes the serine protease inhibitor *LEKTI* (lymphoepithelial Kazal-type related inhibitor), which is mainly expressed in the lamellar granule system of epithelial and lymphoid tissues. This results in severe disruption of skin barrier function and immune paresis. There is a predisposition to food allergies with markedly raised IgE levels and eosinophilia.

Clinical Features

Symptoms

The infant is born with a generalized, exfoliative erythroderma and there may be serious complications in the neonatal period from hypernatraemia, dehydration from increased transient water loss and failure to thrive with decreased albumin due to high skin turnover. Temperature instability, cardiac failure and repeated skin, respiratory tract and systemic infections are common.

Morphology

Most present with erythroderma and scaling (which simulates non-bullous congenital ichthyosiform erythroderma) or continuous skin peeling, which is followed by a very specific change known as *ichthyosis linearis circumflexa*, which is a red, slightly scaly annular or polycyclic patch that migrates outwards and has a characteristic incomplete, double-edged, scaly margin (Fig. 20.23). This occurs from the first year onwards. In severely afflicted patients, generalized ichthyosis and erythroderma persist.

Distribution

The erythroderma is universal but the face and flexures may be involved and is usually misdiagnosed as atopic eczema.

The hair changes (Fig. 20.24) usually, but not always, appear in infancy and are diagnostic. The scalp and eyebrow hairs are short and brittle. Trichorrhexis invaginata is pathognomonic (Fig. 20.25) but pili torti and trichorrhexis nodosa may occur.

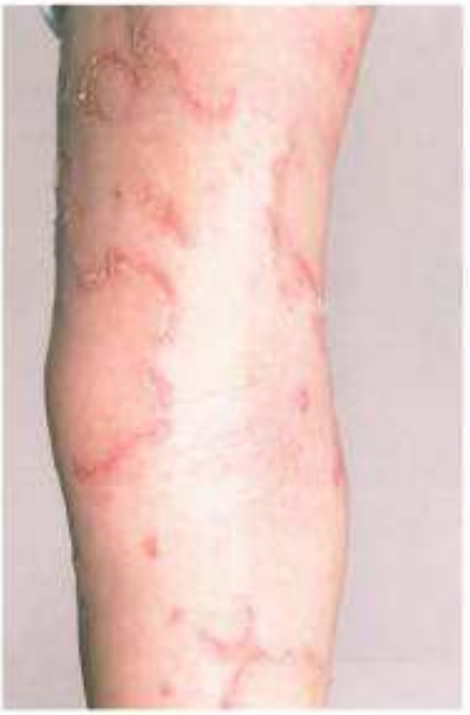


Fig. 20.23 Netherton's syndrome.
Red, polycyclic or annular patches migrate outwards with a characteristic incomplete, double-edged scaly margin, known as ichthyosis linearis circumflexa.

Histopathology

Hyperkeratosis is mild, unlike other ichthyoses, and parakeratosis limited or absent. The granular cell layer is present at the periphery of the lesion. Ultrastructurally, inclusion bodies have been recognized in a suprabasal keratinocyte and abnormalities in the tonofilament–keratohyalin structures, desmosomes and lamellar bodies.

Management

The differential diagnosis in infancy is from erythrodermic psoriasis, non-bullous ichthyosiform erythroderma (although Netherton's syndrome never has a collodion membrane at birth), acrodermatitis enteropathica and immunodeficiency in particular. *Omenn's syndrome* is a rare autosomal recessive combined immunodeficiency presenting as neonatal erythroderma, diffuse alopecia, lymphadenopathy, hepatosplenomegaly, recurrent infections, diarrhoea and failure to thrive. There is eosinophilia, lymphopenia, malfunctioning T cells, absent B cells, reduced IgA and IgG, raised IgE and reduced albumin. Bone marrow transplantation is often necessary. The condition is due to faulty VDJ recombination, which results in the arrest of T and B cell development and eventually, therefore, humoral and cellular immunodeficiency. *RAG* genes are expressed in immature lymphocytes and initiate recombination of variable (V), diversity (D), and joining (J) segments of immunoglobulins and T cell receptors that represent the wide diversity of the immune system.

The absence of the LEKTI protein on molecular testing or immunostaining of the skin is diagnostic. The 'bamboo' nodal dilatation formed from the invagination of one part of the hair shaft to another is the clue to diagnosis and may be found in scalp or eyebrow hair.

The use of topical steroids should be avoided because there is a propensity to develop iatrogenic Cushing's syndrome and Netherton's syndrome is aggravated by retinoids, in contrast to other ichthyosiform erythrodermas. Pimecrolimus may be helpful, but similar caution should be exercised regarding systemic absorption.

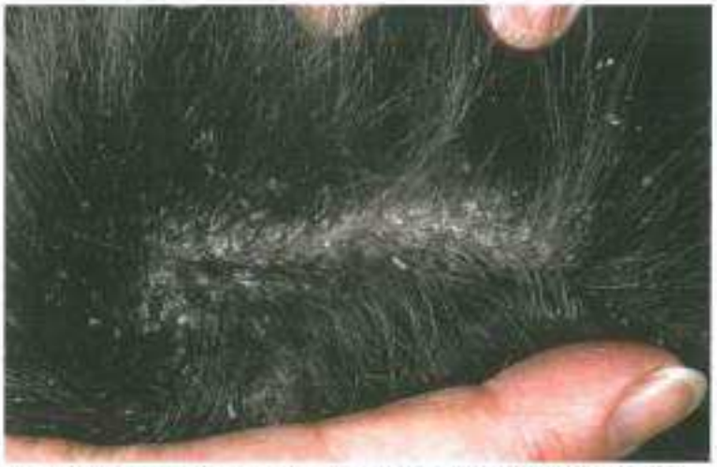


Fig. 20.24 Netherton's syndrome. Trichorrhexis invaginata is pathognomonic but pili torti and trichorrhexis nodosa occur.

Fig. 20.25 Trichorrhexis invaginata. This is also known as bamboo hair because of a ball and socket appearance along the hair shaft or 'golf tee' nodule made up of the broken hair shaft. (With permission from Bolognia JL, Jorizzo JL, Rapini RP, et al: Dermatology, 2nd edition. London: Elsevier, 2008.)

Keratosis pilaris

A common disorder of keratinization of the hair follicles that is most prominent on the extensor surfaces of the proximal limbs.

Aetiology

It temporarily affects many adolescents, when it may be regarded as being physiological. Others have the tendency from childhood, when it is dominantly inherited, and the disorder persists into adult life. It is a follicular form of ichthyosis. The orifice of the hair follicle is distended by a keratin plug, which may contain a hair. It frequently occurs in association with the dominant form of ichthyosis vulgaris. It tends to be worse in the winter and better in the summer.

It is associated with systemic steroid therapy, Cushing's, Down's and Noonan's syndromes. It also occurs in gross nutritional deficiency (when it is known as *phrynoderma*), classically vitamin A deficiency with night blindness, conjunctival and corneal lesions, but also vitamin B, E, and essential fatty acid deficiency. It may occur with malabsorption (e.g. small bowel bypass surgery, pancreatic insufficiency and chronic giardia) and inadequate diet resulting in comedone-like horny plugs on the elbows, thighs and buttocks. The adjacent skin is scaly and pigmented.

Clinical Features

Symptoms

Rough skin or goose flesh occurs.

Morphology

Discrete, small, grey, horny, rough, perifollicular papules form, sometimes surrounded by erythema (Fig. 20.26).

Distribution

The papules occur on the posterolateral aspects of the upper arms (Fig. 20.27) and thighs and sometimes cheeks or more extensively (Fig. 20.28).

Fig. 20.26 Keratosis pilaris. The posterolateral aspects of the upper arms and thighs are the characteristic sites. The condition is often physiological in adolescence but it may be inherited.

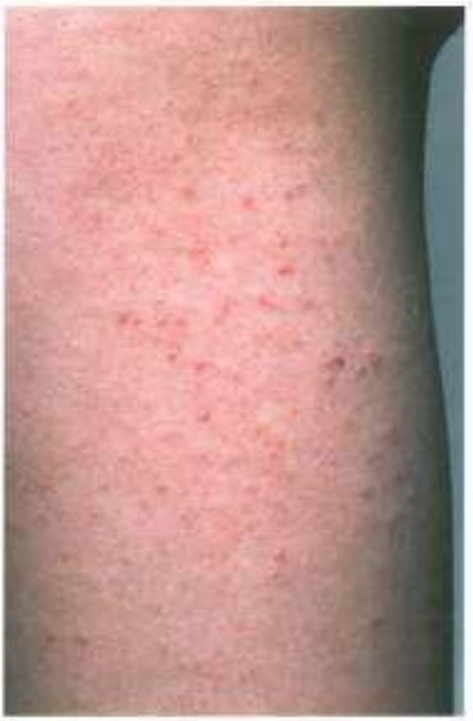


Fig. 20.27 Keratosis pilaris. Discrete, small, grey, horny perifollicular papules occur, sometimes surrounded by erythema.

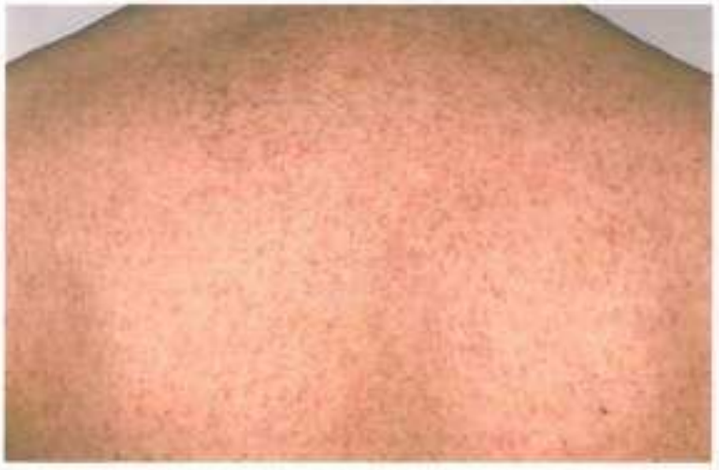


Fig. 20.28 Keratosis pilaris. The disorder may be extensive. There is no effective treatment.

Fig. 20.29 Lichen spinulosa. This is a temporary variant of keratosis pilaris. Round or oval patches of minute, follicular papules with a horny spinous centre occur, particularly in boys.

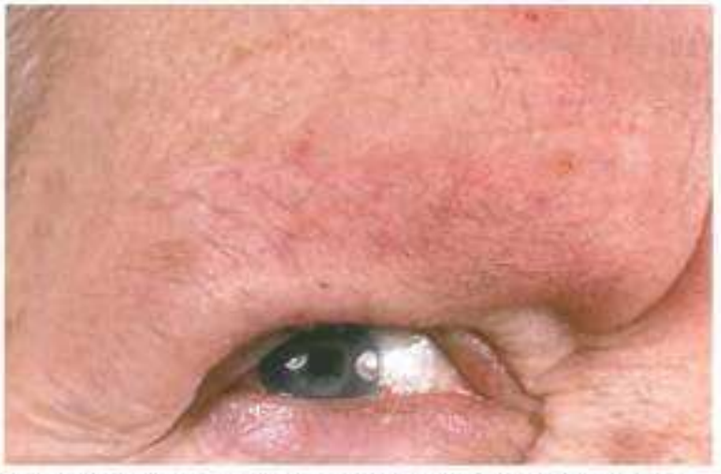


Fig. 20.30 Ulerythema ophryogenes. There is erythema and atrophy of the eyebrows, often with keratotic papules. It is persistent but of no consequence.

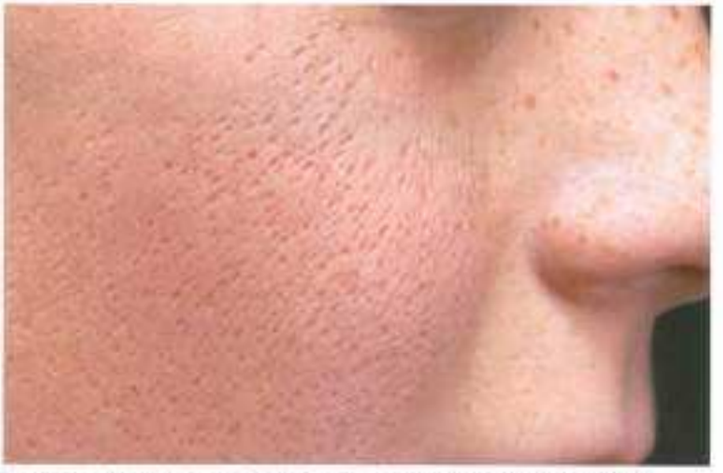


Fig. 20.31 Atrophoderma vermiculatum. A reticulate atrophy follows the follicular plugging. (Courtesy of the Institute of Dermatology.)

Management

The appearance is characteristic and treatment is ineffective. Other similar conditions include:

Keratosis spinulosa (lichen spinulosa) is a temporary variant most frequently seen in boys. It consists of round or oval patches of up to 5 cm in size that are made up of minute follicular papules with a horny spinous centre (Fig. 20.29). They tend to extend for a few days and then remain stationary for a while before clearing. They occur symmetrically on the neck, buttocks, abdomen, popliteal fossae and extensor surfaces of the arms.

Keratosis pilaris atrophicans faciei (ulerythema ophryogenes) is an atrophic variant where there is erythema and small horny plugs at the outer aspects of the eyebrows initially, which extend medially to destroy the hair follicles (Fig. 20.30). It begins at birth or in early infancy. If it affects the cheeks, it is known as *atrophoderma vermiculatum* (Fig. 20.31).

Keratosis follicularis spinulosa decalvans is an extensive keratosis pilaris with a scarring alopecia affecting the scalp from infancy or childhood; it may affect the face, extremities or be quite generalized. It is usually sporadic but may be quite severe in males and be X-linked. There may be corneal opacities, photophobia and limited keratoderma.

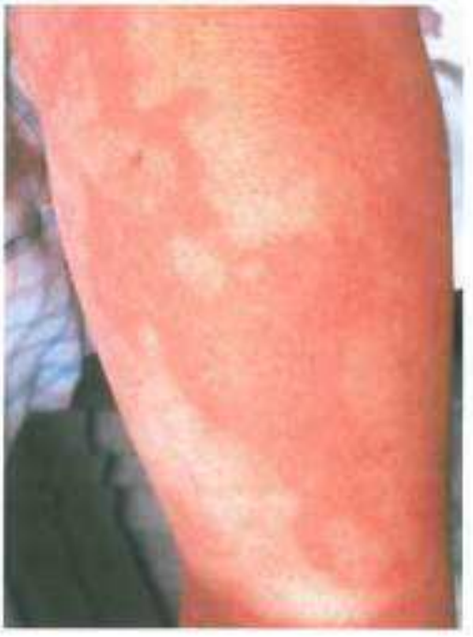


Fig. 20.32 Erythrokeratoderma variabilis. A migratory erythema appears and regresses over a very short interval. (Courtesy of Dr David Atherton.)

Erythrokeratoderma variabilis

Erythrokeratoderma variabilis is a rare autosomal dominant disease that is present at birth or may occur within the first year. It was described by Mendes da Costa. There are mutations in the GJB3 and 4 genes, localized to chromosome 1p34-35. These encode the connexin proteins 31 and 30.3 respectively, which are expressed on differentiated keratinocytes. These are transmembrane proteins involved in intercellular gap junction activity mediating metabolic and electrical communication between cells. They are therefore essential for epidermal differentiation and function. The erythrokeratodermas are clinically heterogeneous and may be generalized or localized. There are two morphological features, a transient figurate, striking migratory erythema (Fig. 20.32) that appears or regresses over a matter of minutes or hours, or a more stable hyperkeratotic variety.

Palmar-plantar keratoderma

A diverse group of inherited or acquired pronounced thickening of the skin of the palms and soles, which may occur in a diffuse, linear or punctate manner.

Aetiology

Palmar-plantar keratoderma is not a specific disease but a clinically diverse spectrum of hyperkeratosis of the palms and soles, which may be hereditary (Fig. 20.33) or acquired (Fig. 20.34) and may have additional cutaneous and other features. There is a confusing terminology but this is being clarified by the identification of specific genetic abnormalities in the structural proteins in the keratinocytes.

Broadly, palmar-plantar keratoderma may be classified by:

- mode of inheritance
- morphology, i.e. diffuse, focal (oval on palms, striate or linear on palms) and punctate (1 mm to 1 cm keratotic papules)
- distribution, i.e. palms, soles or transgressing onto dorsal and flexor surfaces
- involvement of other ectodermal structures
- presence or absence of non-ectodermal structures, e.g. deafness, cardiomyopathy
- microscopic changes either light (e.g. epidermolytic in keratin 9 mutations) or electronmicroscopy
- mutations in:
  - keratins (K9 in diffuse epidermolytic hyperkeratotic type, K14 in Naegeli–Franceschetti–Jadassohn syndrome)
  - loricrins, which are proteins of the cornified cell envelope, e.g. Vohwinkel-variant syndrome, where there is mutilating palmar-plantar keratoderma
  - desmogleins and desmoplakins (cohesion molecules), e.g. striate palmar-plantar keratoderma and Carvajal syndrome (palmar-plantar keratoderma, woolly hair and potentially fatal cardiomyopathy due to desmoplakin and plakoglobin mutations
  - connexins (intercellular communication), e.g. mutilating palmar-plantar keratoderma and deafness (Vohwinkel syndrome), hidrotic ectodermal dysplasia (connexin 30), keratitis ichthyosis deafness (KID) syndrome and erythrokeratoderma variabilis
  - cathepsin C (transmembrane conduction), e.g. Papillon–Lefèvre
  - *SLURP1* (transmembrane conduction, cell activation and adhesion, e.g. mal de Meleda.

The congenital diffuse type is inherited as an autosomal dominant, occurs in early infancy or slightly later and is seen particularly in Sweden (*Thost–Unna type*). There is often pronounced hyperhidrosis, pitted keratolysis and dermatophytosis. It has been possible to separate off a variety that is clinically identical but histologically shows epidermolytic hyperkeratosis and is caused by a defect on chromosome 17 giving rise to a mutant keratin 9. There is a rare condition often associated with consanguinity known as *mal de Meleda* (an island off the Dalmatian coast) that is more extensive, involves the backs of the hands and is malodorous. There is usually perioral erythema.

The diffuse type may occur with associated abnormalities. *Vohwinkel syndrome* is a mutilating condition, which may be associated with deafness. *Bart–Pumphrey syndrome* has in addition to palmar-plantar keratoderma, knuckle pads, leuconychia and sensorineural deafness. *Naxos syndrome* has woolly hair and an arrhythmogenic cardiomyopathy. Focal keratodermas include *pachyonychia congenita*, where there is a striking, wedge-shaped deformity of the nails and other abnormalities and keratoderma of weight-bearing areas. A similar pressure-point keratoderma occurs in *tylosis*, which is a familial disorder associated with oesophageal carcinoma. The *TOCT* (tylosis with oesophageal cancer) locus is found on chromosome 17q23(3). This is a familial disorder; the keratoderma appears in later life and is often associated with keratopilaris and oral leucokeratosis.

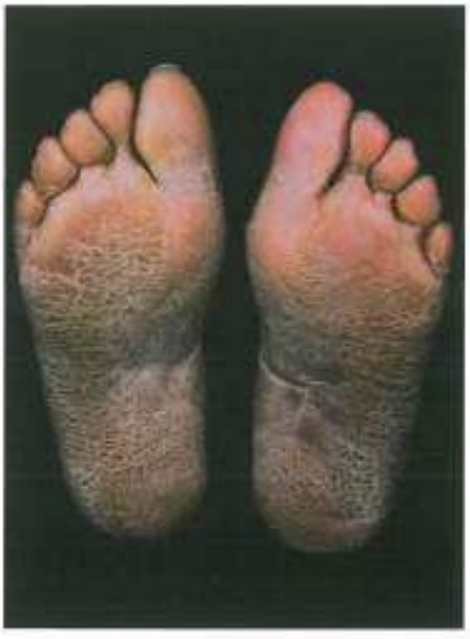


Fig. 20.33 Palmar-plantar keratoderma. The skin is markedly thickened and often has a yellow tint. The keratoderma is symmetrical.

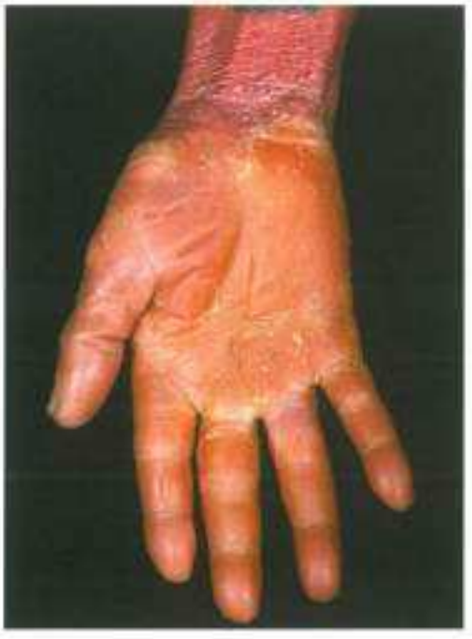


Fig. 20.34 Pityriasis rubra pilaris. Palmar-plantar keratoderma may be acquired, for example in Sézary syndrome, malignant acanthosis nigricans, tylosis and pityriasis rubra pilaris.

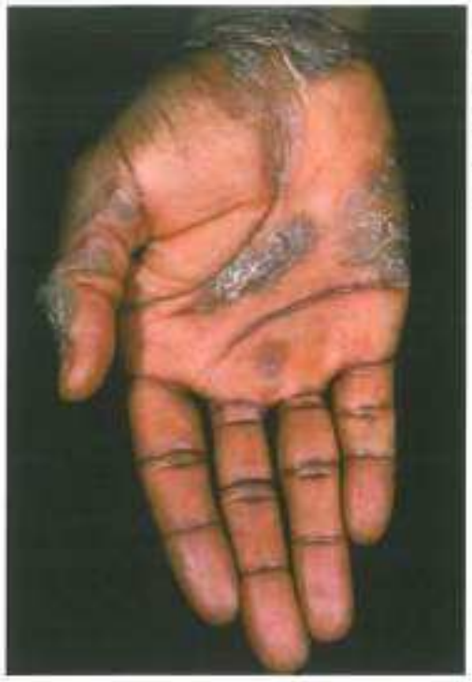


Fig. 20.35 Striate keratoderma. The localized forms of palmar-plantar keratoderma may be punctate or linear in distribution. Striate forms are due to disruption of desmoglein 1.

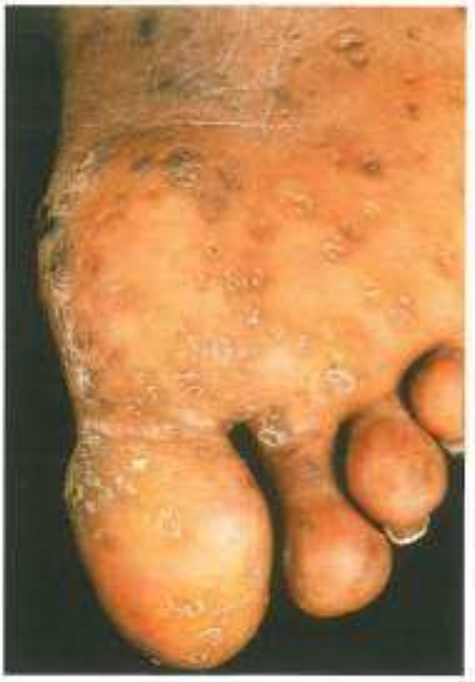


Fig. 20.36 Punctate keratoderma. Punctate forms of keratoderma occur, particularly in black skins, and are inherited.

Destructive changes may occur including in *Olmsted's syndrome*, which is a congenital palmar-plantar and perioral keratoderma. The keratoderma is sharply defined with concomitant erythema. Flexion deformities of the digits occur, resulting in constriction or spontaneous amputation of digits. It occurs only in males and there is a very characteristic erythema and warty keratosis around the mouth.

In the *Papillon–Lefèvre syndrome*, there is redness in association with the hyperkeratosis of the palms and soles, which is usually quite diffuse. There is periodontosis, with loss of dentition, and frequent pyogenic infections as a result of disordered leucocyte function. It is an autosomal recessive disorder. There is often consanguinity. Acitretin before the age of four permits normal dentition.

Hydrotic ectodermal dysplasia is discussed later in this chapter.

The localized types may be striate (Fig. 20.35) or punctate (Fig. 20.36). There are often variations within individuals or families but genetic linkage studies are likely to clarify the whole problem. They are certainly quite common in Afro-Caribbeans and are inherited as an autosomal dominant. In one variety, small hyperkeratotic papules occur in the palmar creases (Figs 20.37 and 20.38) or on the soles.

Another common condition in black skins is *acrokeratoelastoidosis*. Small, firm, pearly or warty papules, which may become confluent (Fig. 20.39), occur along the borders of the hands (Fig. 20.40) and wrists and along the sides of the fingers, feet and ankles. The condition may be associated with a hyperkeratosis of the palms and soles, hyperpigmentation and hyperhidrosis.

Localized, well-defined areas of thickening of the skin over the interphalangeal and metacarpal phalangeal joints (Fig. 20.41) are known as *knuckle pads*. They are most common in black skins and commence in adolescence. They are inherited as an autosomal dominant. They are occasionally associated with palmar (Dupuytren's) or plantar (Lederhose's) fibromatosis and penile (Peyronie) fibromatosis.

Punctate keratoses are seen in association with previous arsenic ingestion and with malignancy; they may occur in association with bladder and lung cancer, possibly in association with smoking or with the human

Fig. 20.37 Palmar pits. Fine dark pits occur in the skin creases of Afro-Caribbeans and Afro-Americans. Many regard them as a normal variant.

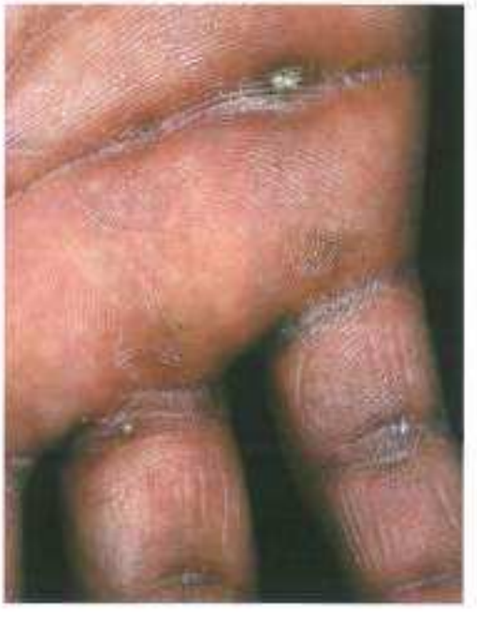


Fig. 20.38 Palmar pits. Discrete hyperkeratotic papules occur in the palmar creases and are known as palmar pits. They can be quite uncomfortable.

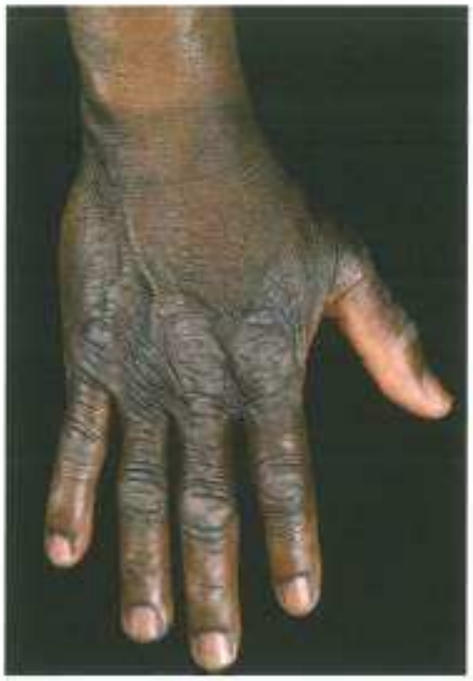


Fig. 20.39 Acrokeratoelastoidosis. Not uncommon in black skins, warty papules may occur along the sides of the fingers and tend to coalesce over the backs of the hands.

Fig. 20.40 Acrokeratoelastoidosis. The hyperkeratotic plaques along the sides of the finger are characteristic.

papillomavirus. Other associations with malignant disease include the tripe palms of malignant acanthosis nigricans and the scaling and sometimes hyperkeratosis of the tips of fingers and nailfolds with involvement of the nose and conchae of the ears in Basex syndrome. These are acquired forms of keratodermas.

Keratoderma climacterium is a disorder of middle-aged women who are often obese. Circumscribed, discrete, round or oval patches of keratoderma occur that slowly increase in thickness and extent; they occur commonly in the mid-palm, around the margins of the heel and across the sole behind the line of the metatarsal heads. This condition tends to persist for a long period of time, although it may ultimately resolve. Acquired keratoderma may also very rarely occur in myxoedema.

Clinical Features

Symptoms

The symptoms vary but in all forms are uncomfortable and interfere with manual dexterity.

Morphology and distribution

The eruption is symmetrical and very well defined, with abrupt borders at the sides of the hands and fingers or feet. The skin is excessively thick and often a slightly yellow colour. It feels rough, tends to crack (Fig. 20.42) and becomes painful, especially in the winter months.

Management

This is difficult if a cause cannot be established. Calcipotriol, various emollients, 40% propylene glycol in aqueous cream and a variety of salicylic acid-based preparations may be used. Oral retinoids are used in some cases.

The common conditions that must be distinguished include psoriasis, Reiter's syndrome, pityriasis rubra pilaris, eczema, lichen planus, lupus erythematosus (rarely) and other congenital diseases such as Darier's disease, dyskeratosis congenita, hydrotic ectodermal dysplasia and the Dowling–Meara form of epidermolysis bullosa.

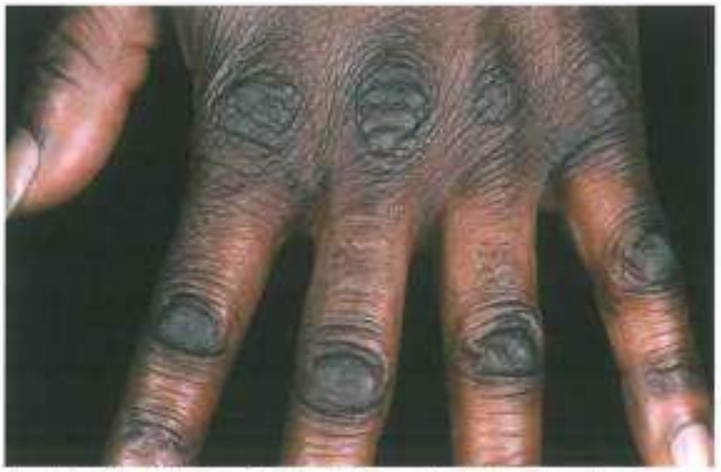


Fig. 20.41 Knuckle pads. There is thickening of the skin overlying the interphalangeal joints.

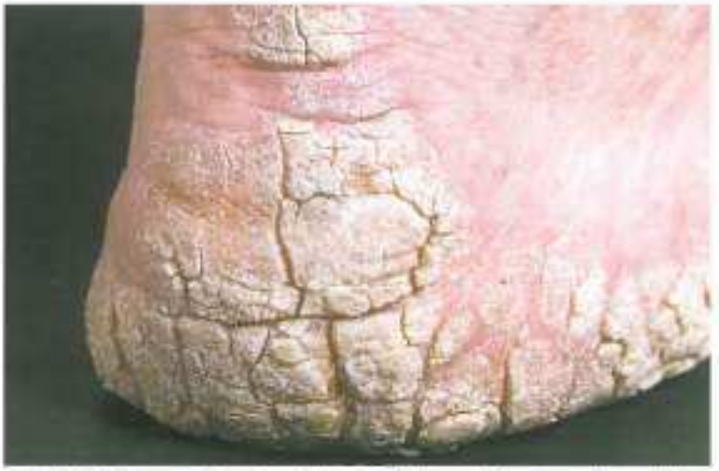


Fig. 20.42 Palmar-plantar keratoderma. The hyperkeratosis may fissure in dry, cold weather. There is an abrupt end to the eruption at the side of the foot.

Pityriasis rotunda

A distinctive, clinical appearance of round, dry patches on the skin and probably represents an acquired pseudoichthyosis.

Aetiology

Its cause is unknown. It is more common in the Far East, particularly Japan, and in Africa. The histology shows a reduced or absent granular cell layer, pigmentation of the basal layer with some pigmentary incontinence and a slight perivascular infiltrate. It usually starts in the third or fourth decade. It has been described with tuberculosis or malignancy (particularly adenocarcinoma of the bowel).

Clinical Features

Symptoms

Asymptomatic round patches appear.

Morphology

It consists of perfectly round, dry (Fig. 20.43), scaling, very well-defined patches of up to 3 cm or more in diameter.

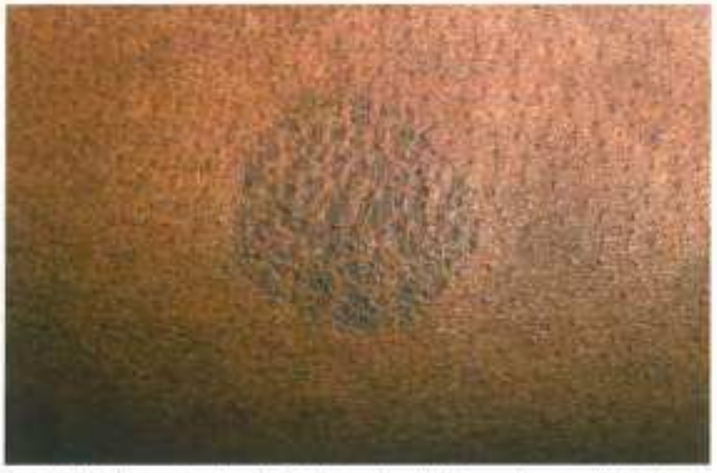


Fig. 20.43 Pityriasis rotunda. The lesion is perfectly round, very well defined, dry and scaly. It is an acquired pseudoichthyosis. It is virtually confined to darker skins.

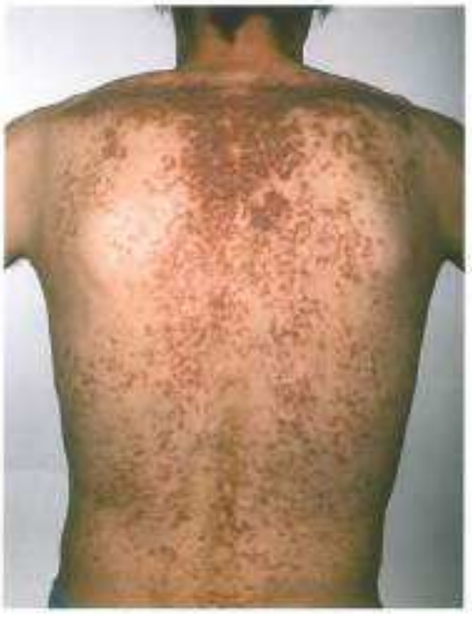


Fig. 20.44 Darier's disease. The back is affected but the buttocks are spared. The gene *ATP2A2* is widely expressed and encodes a calcium pump.

Distribution

They may be solitary or multiple and have been described on the buttocks, thighs, abdomen, back or upper arms.

Management

Skin scrapings should be taken to exclude a fungal infection, and a skin biopsy is useful to exclude cutaneous T cell lymphoma. There is no treatment. It may improve in the summer, but generally persists for many years.

Darier's disease

An autosomal dominant disorder of epidermal cell cohesion characterized by acantholysis and premature partial keratinization and clinically by characteristic warty papules.

Aetiology

Darier's disease (*keratosis follicularis*) is caused by mutations in the endoplasmic reticulum ATPase *ATP2A2* gene localized to the 2 cM region of chromosome 12 at 12q23-24.1. This region encodes SERCA2, a widely expressed calcium pump. Dysfunction leads to acantholysis and apoptosis.

There is imperfect formation and maturation of the tonofilament–desmosome complex and the epidermal cells do not adhere together properly. As a result, acantholysis and splitting occurs in the epidermis and keratin is formed incorrectly and prematurely.

Patients are usually partially immunodeficient and this probably explains their susceptibility to secondary bacterial infection and to extensive herpes simplex infection and other viruses including vaccinia, cowpox and Coxsackievirus A16.

The cutaneous findings are quite varied and very mild forms exist; consequently, a so-called sporadic case may in fact be familial. There are variants of classical Darier's disease (Fig. 20.44) that include hypertrophic, vesiculo-bullous and linear manifestations. The linear variant (Fig. 20.45) is a genetic mosaicism of generalized Darier's disease and mutation of *ATP2A2* has been shown in affected skin DNA but not in DNA from normal skin or peripheral white cells.

Clinical Features

Symptoms

The rash begins in late childhood or adolescence.

Morphology

Symmetrical, small, firm, red-brown papules (Fig. 20.46) with greasy, crusted or warty surfaces may coalesce into plaques. Vesiculo-bullous lesions may occur and malodorous hypertrophic vegetation with secondary bacterial sepsis may occur, particularly in the flexures.

Distribution

Similar to seborrhoeic dermatitis, the rash occurs on the face (especially the forehead and ears), scalp, front (Fig. 20.47) and back of the trunk and flexures. There is a cut-off at the sacrum without involvement of the buttocks. Although flexural involvement does occur in most patients, this may be the dominant site in the minority of patients.

Skin-coloured, warty, flat-topped papules (Fig. 20.48) may occur on the backs of the hands and feet and on the knees, elbows and forearms. Pits on the palms are a characteristic feature (Fig. 20.49), and the palms and soles may be focally or diffusely hyperkeratotic.

The nails (Fig. 20.50) are generally affected and broad, white or slightly translucent red, longitudinal bands may occur. A tendency for nails to

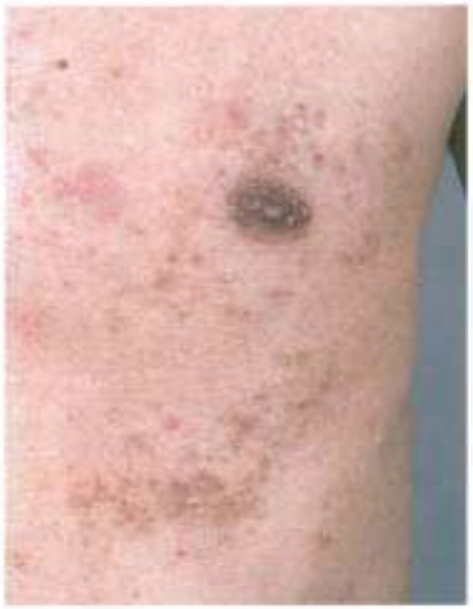


Fig. 20.45 Darier's disease (linear variant). Darier's disease may occur in a zosteriform distribution. Biopsy established the diagnosis. It is a genetic mosaicism of the generalized disease.

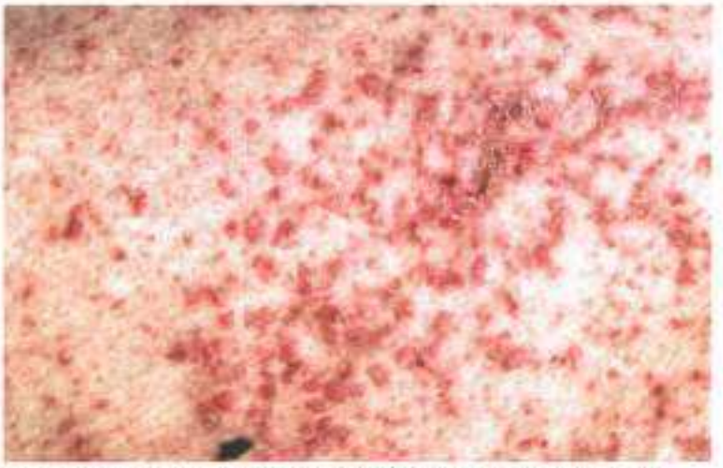


Fig. 20.46 Darier's disease. There are symmetrical, small, firm, red-brown papules, which on close inspection may show fine fissures in their surface.

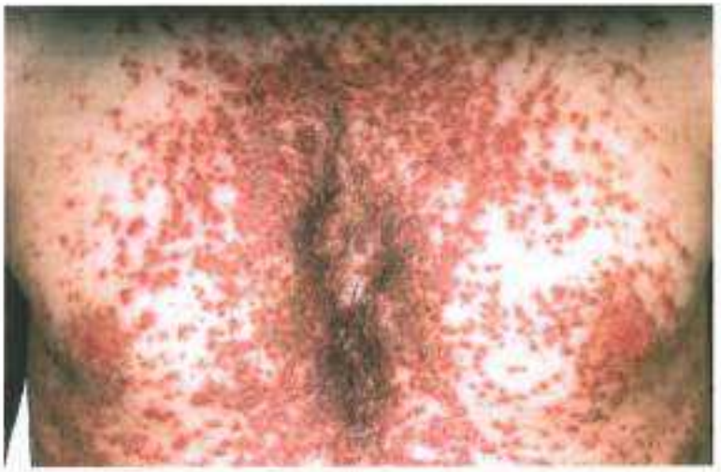


Fig. 20.47 Darier's disease. The distribution is similar to that of seborrhoeic dermatitis. This outbreak was exacerbated by exposure to sunlight. It responded well to acitretin.

Fig. 20.48 Darier's disease. Skin-coloured, flat-topped, warty papules may occur on the backs of the hands.

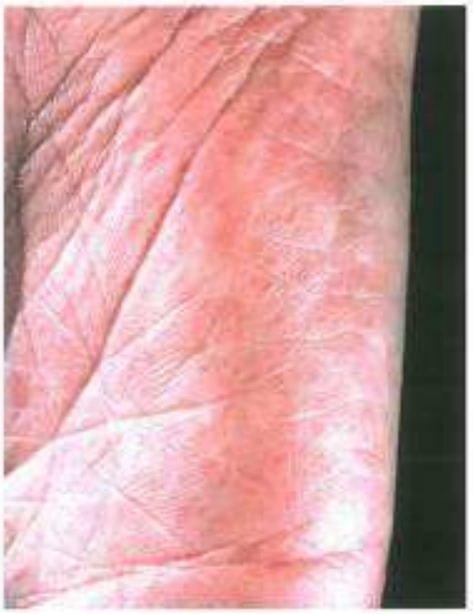


Fig. 20.49 Darier's disease. Palmar pits are a characteristic feature.

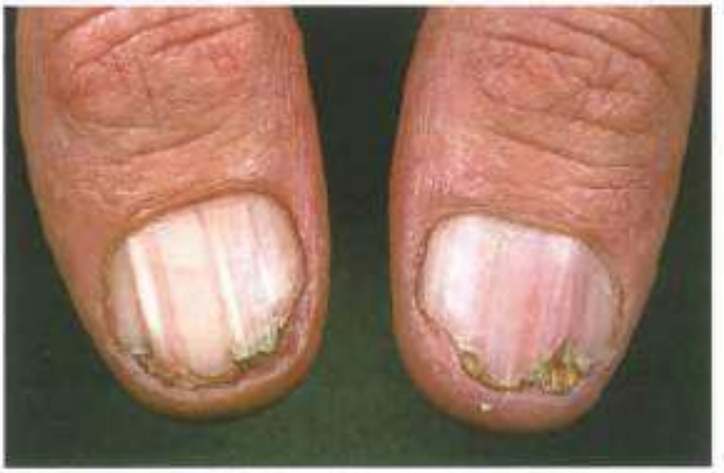


Fig. 20.50 Darier's disease of the nails. There are notches at the distal end of the nails, which are thin and friable with alternating red and white lines.

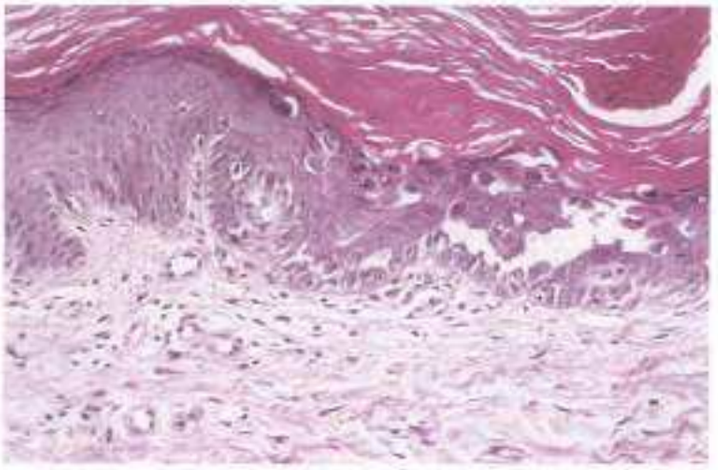


Fig. 20.51 Darier's disease. Suprabasal acantholysis has resulted in a cleft-like vesicle. Note the conspicuous parakeratotic tier on the far right.

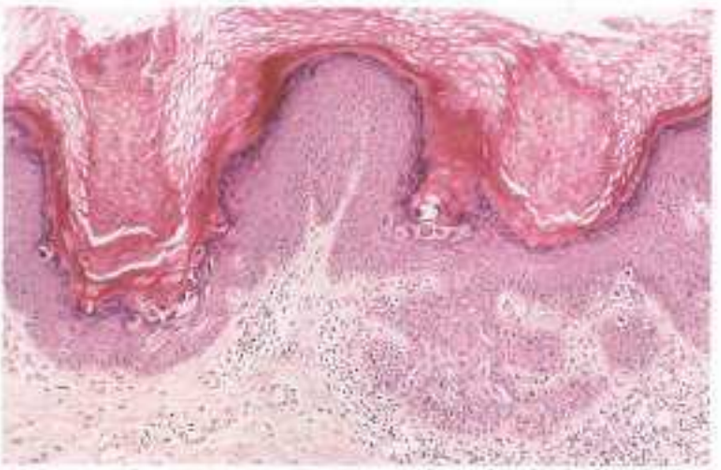


Fig. 20.52 Darier's disease. There is dyskeratosis, acantholysis and hyperkeratosis with a prominent parakeratotic tier. Several keratinocytes show marked cytoplasmic vacuolation and abnormal nuclei (corps ronds) in the upper prickle cell and granular cell layers.

break at their distal margin and produce a V-shaped notch is diagnostic. The nail changes may occur in isolation.

Fine white papules may occur on the hard palate, and the mucosa sometimes has a cobblestoned appearance.

Histopathology

There is irregularly distributed suprabasal clefting (Fig. 20.51), which leads to acantholysis and abnormal keratinization. Some of the cells are quite large, with darkly staining nuclei and a clear cytoplasm, and are known as 'corps ronds' (Fig. 20.52) and as the cytoplasm shrinks and the cells become smaller, known as 'grains'. The surrounding epidermis is acanthotic, parakeratotic and hyperkeratotic. The hair follicles, sweat ducts and mucous salivary glands are similarly affected. Salivary gland obstruction may occur. Ultrastructurally, the tonofilaments become separated from the desmosomes, with vacuolation in the cytoplasm. Immunofluorescence studies are usually negative.

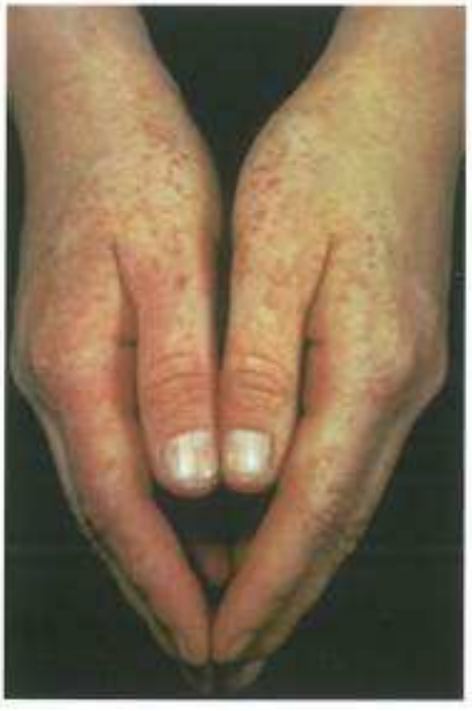


Fig. 20.53 Acrodermatitis verruciformis of Hopf. Numerous, flat-topped papules are present on the extremities. The histology is different from that of Darier's and lesions may transform into squamous cell carcinoma.

Management

A skin biopsy should be performed to confirm the diagnosis. The condition is chronic and does not go into remission, but exacerbations may occur in response to ultraviolet light exposure (which should be avoided) and to sepsis. Secondary bacterial infection should be treated with antibacterial drugs. Potent steroids, combined with antibiotics, are generally helpful. Occasionally, generalized herpes simplex (Kaposi's varicelliform eruption) may occur and systemic acyclovir is indicated. Oral retinoids are partially effective and may be necessary, particularly intermittently, but this must be weighed against the long-term side-effects, which include diffuse idiopathic spinal hyperostosis. Epilepsy occurs in 4% of patients.

The diagnosis of Darier's disease is not difficult. Acral Darier's disease, however, can sometimes be clinically confused with *acrokeratosis verruciformis of Hopf* to which it is identical clinically (Fig. 20.53). Histologically, the latter consists of hyperkeratosis, a prominent granular layer, papillomatosis and discrete pointed epidermal upgrowths resembling a church spire, which is quite different from Darier's disease, but mutations in *ATP2A2* have been found and it may represent a Darier variant. It usually presents at birth, is dominantly inherited and its importance is that the papules can sometimes transform into squamous cell carcinomas.

Hailey–Hailey disease

A dominantly inherited condition resulting in blisters, erosions, fissures and crusts in intertriginous areas.

Aetiology

There are mutations in the gene *ATP2C1* on chromosome 3q21-24, which encodes a Golgi-associated Ca^{2+} ATPase, thus interfering with intracellular Ca^{2+} signalling. There are abnormalities in the tonofilament–desmosome–keratin complex, so epidermal cells do not bind together strongly and are vulnerable in areas of friction. As a result, flaccid blisters, erosions and crusts occur, rather like those seen in pemphigus, which Hailey–Hailey disease resembles histologically.

Clinical Features

Symptoms

It usually commences in adolescence with itchy flexural blistering.

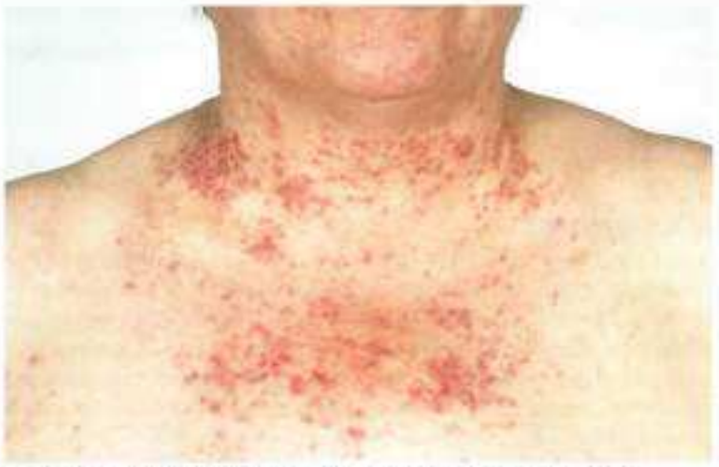


Fig. 20.54 Hailey–Hailey disease. Any area subject to trauma (including ultraviolet light) or friction may be affected since epidermal cells do not bind together effectively owing to abnormalities in the tonofilament–desmosome–keratin complex.

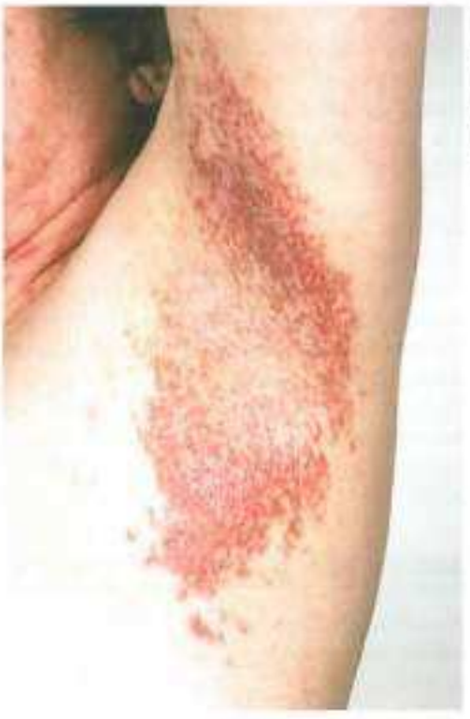


Fig. 20.55 Hailey–Hailey disease. The skin becomes macerated and fissured and ultimately hypertrophic and malodorous.

Morphology

Clear vesicles occur that become turbid, eroded and crust. They extend outwards. Centrally, the lesions may become macerated and fissured.

Distribution

Friction is an important precipitant so any area subject to trauma such as the sides of the neck (Fig. 20.54), axillae (Fig. 20.55), groins (Fig. 20.56) and under the breasts are particularly affected and may become hypertrophic and malodorous with soft, moist vegetations.

The mouth is rarely involved but the nails can be affected with longitudinal bands.

Histopathology

There is considerable acantholysis, which produces suprabasal clefting, but usually it is incomplete and the cells retain some of their connections; as a result, an appearance often likened to a dilapidated brick wall occurs (Fig. 20.57). The adnexal epithelium is usually spared. Immunofluorescence is negative in Hailey–Hailey disease unlike, of course, pemphigus. There are fewer grains and corps ronds and more suprabasal clefting and acantholysis than in Darier's disease.

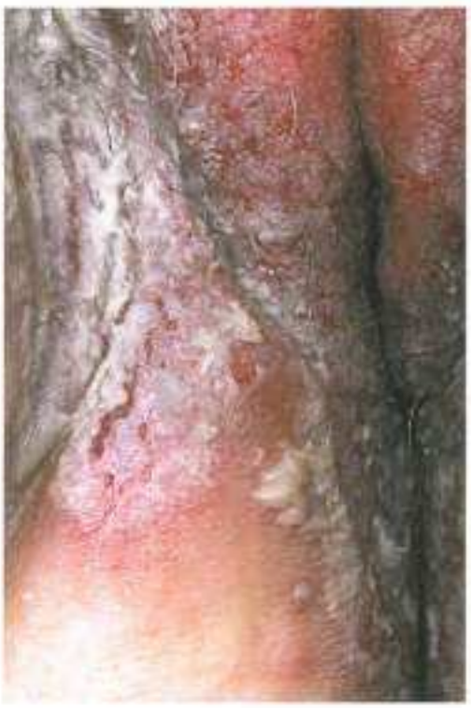


Fig. 20.56 Hailey–Hailey disease. The maceration and the fissuring are particularly obvious in her groin. A biopsy is necessary to establish the diagnosis.

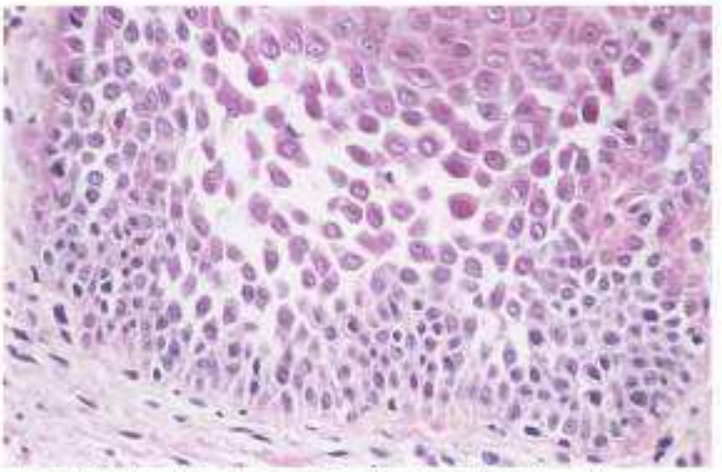


Fig. 20.57 Hailey–Hailey disease. The pathology has been likened to a 'dilapidated brick wall'. This degree of acantholysis with partial retention of cellular orientation is virtually pathognomonic of the disease.

Management

The condition remits and relapses and, unlike Darier's disease, may disappear with age. Despite the clinical and histological overlap with Darier's disease, the finding of different genes does separate the two conditions and probably the basis of flexural Hailey–Hailey disease coexisting with Darier's disease is in fact flexural Darier's disease and not Hailey–Hailey disease.

Ultraviolet light, friction from obesity and infection are important exacerbating factors. The first two should be avoided and swabs taken and appropriate antibacterial or anticandidal agents prescribed if indicated. Herpes simplex superimposition may occur. Allergic contact dermatitis, particularly to topical medicaments, is a feature. Potent topical steroids are effective, although it is not known why. In severe cases, affected skin in the groins or axilla may be excised and grafted. Dermabrasion and laser ablation have been tried successfully. Superficial X-ray therapy may be helpful. Retinoids are not effective but ciclosporin orally and tacrolimus topically may be of benefit.

Transient and persistent acantholytic dermatosis

Also known as *Grover's disease*, it is either an acute, transient, or persistent papulo-vesicular eruption of the trunk characterized by focal acantholytic dyskeratosis.

Aetiology

The cause is unknown; solar damage is notable in most patients. It is often precipitated by ultraviolet light, heat or sweating. Ultrastructurally, intradesmosomal separation occurs with a reduction in the number of desmosomes and a perinuclear aggregation of tonofilaments.

Clinical Features

Symptoms

It has a fairly acute onset and may be quite pruritic.

Morphology

Discrete papules or papulo-vesicles, sometimes with a fissured excoriated surface.

Distribution

Particularly the chest (Figs 20.58 and 20.59) and abdomen are affected.

Management

A skin biopsy is helpful but not diagnostic. There is focal acantholytic dyskeratosis (Fig. 20.60). Other blistering disorders, such as pemphigus, can be excluded by negative immunofluorescence, and Hailey–Hailey disease or Darier's disease by the negative family history. In milder cases, symptomatic treatment with potent steroids is all that is required. Systemic retinoids and steroids and topical calcipotriol and calcineurin inhibitors have been used in some patients. The condition may last a few weeks or much longer.

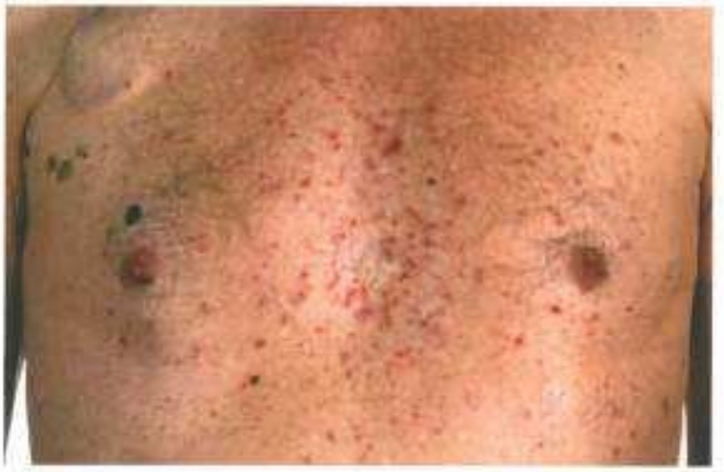


Fig. 20.58 Grover's disease. The lesions occur on the trunk and are discrete itchy papules or papulo-vesicles. It may be more common in males and is related to excess solar exposure.

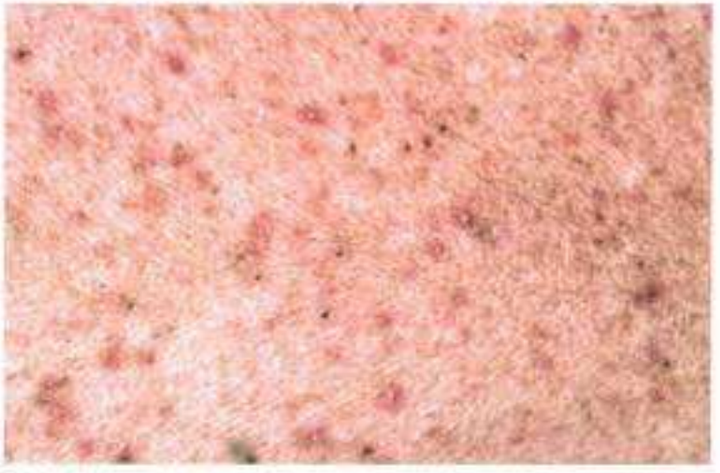


Fig. 20.59 Grover's disease. The lesions are red discrete itchy papules or papulo-vesicles usually in considerable numbers on the front of the chest. They may respond to topical potent steroids or persist.

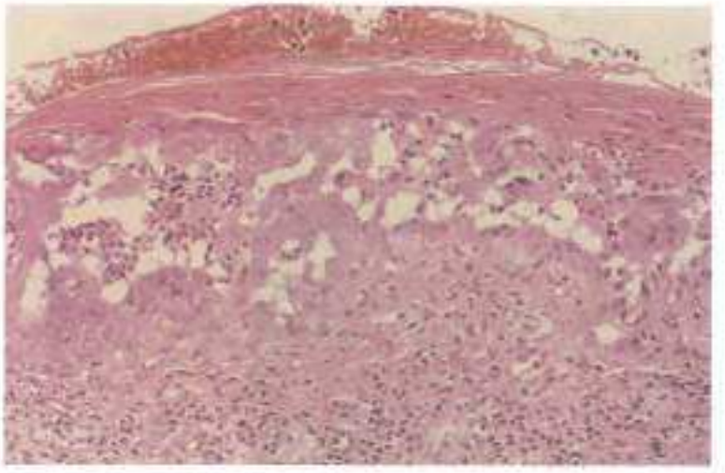


Fig. 20.60 Grover's disease. There is focal acantholytic dyskeratosis, and it therefore mimics Darier's disease.

Perforating keratotic disorders

Transepithelial elimination of dermal material without much disruption of the surrounding structures may occur secondary to granuloma annulare or pseudoxanthoma elasticum or as a primary event in four conditions: Kyrle's disease, perforating folliculitis, elastosis perforans serpiginosa and reactive perforating collagenosis (a rare familial disorder beginning in childhood). These conditions were considered to be separate entities but all have been described in association with diabetes mellitus or in patients with chronic renal failure undergoing haemodialysis and occasionally lymphoma, hepatocellular and prostatic carcinoma, sclerosing cholangiitis and IgA nephropathy and are known in these circumstances as *acquired reactive perforating dermatoses* (Figs 20.61 and 20.62).

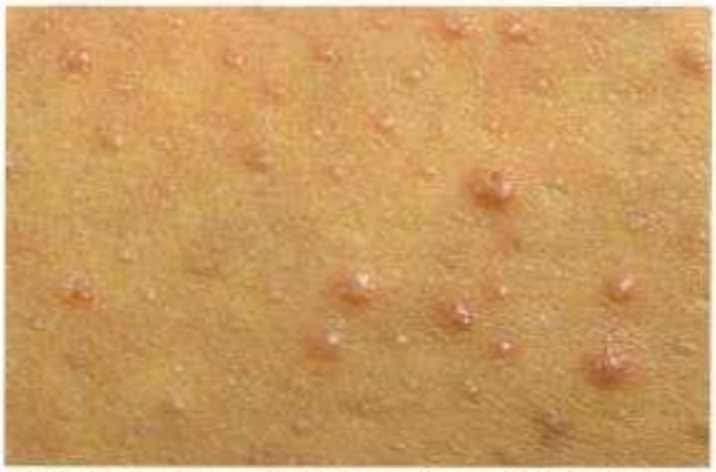


Fig. 20.61 Acquired reactive perforating dermatosis. The lesions are centred around hair follicles and the dermal material is eliminated as a central keratin plug.

Perforating folliculitis occurs on the limbs of young adults; there are small, red, follicular papules that are usually asymptomatic and histologically characterized by a plug of keratin which disrupts the hair infundibulum of the follicular epithelium. *Reactive perforating collagenosis* occurs as a familial event in young people and is probably a reaction to cold or trauma leading to focal damage to collagen and subsequently to its extrusion through the epidermis. It occurs in early childhood. Small papules increase in size and become indented by a keratin plug and subsequently scar; they are found on the hands, elbows or knees. Kyrle's disease and elastosis perforans serpiginosa are sufficiently characteristic and merit separate descriptions.

KYRLE'S DISEASE

Kyrle's disease (*hyperkeratosis parafollicularis*) is a distinctive clinical eruption of follicular plugging, particularly on the legs and forearms.

Aetiology

The aetiology is unknown. It usually commences in middle age and is occasionally associated with diabetes mellitus, chronic renal failure or hyperlipidaemia. A similar condition, but with smaller lesions (Fig. 20.63), is known as *Flegel's disease* (*hyperkeratosis lenticularis perstans*). It occurs in both sexes, is probably inherited as an autosomal dominant and appears in middle years. Many believe them to be a single entity.

Clinical Features

Symptoms

Asymptomatic roughened spots occur on the limbs.

Morphology

A small horny plug up to 1.5 cm in diameter protrudes from a crateriform depression. It is surrounded by a zone of erythema and can be fairly readily removed. One may merge into another to produce polycyclic plaques.

Fig. 20.62 Acquired reactive perforating dermatosis. Follicular papules with a central plug of keratinous material occur in a number of conditions as a result of transepidermal elimination of dermal material; they occur particularly in diabetics with renal failure.

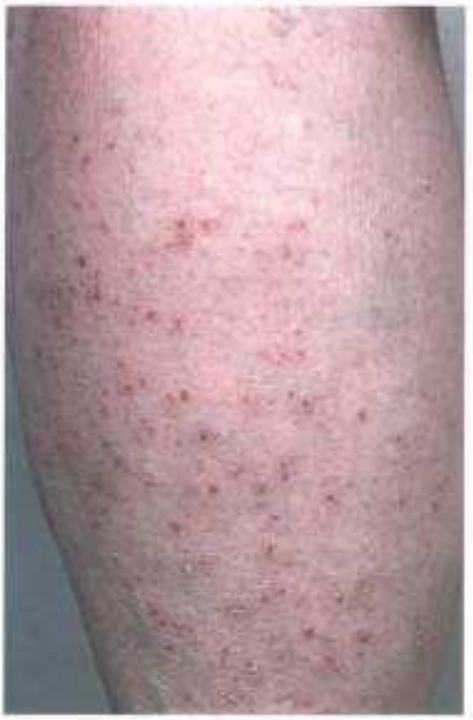


Fig. 20.63 Flegel's disease. There are red-brown papules with a horny adherent scale, which when removed shows a saucer-shaped pinpoint bleeding base. The lesions are smaller than those of Kyrle's disease.

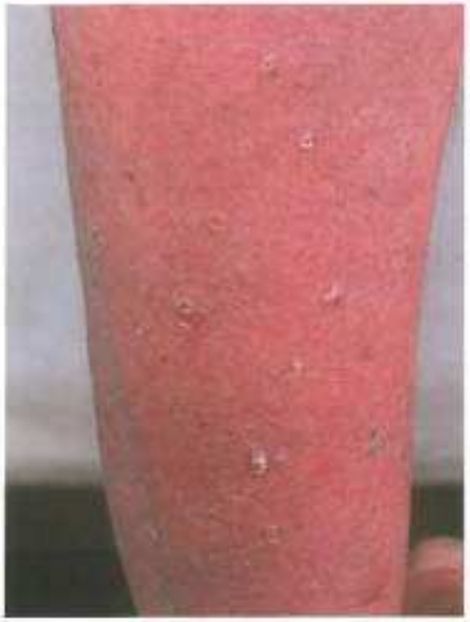


Fig. 20.64 Kyrle's disease. The lesions occur on the limbs and consist of a horny plug that protrudes from a crater, surrounded by erythema.

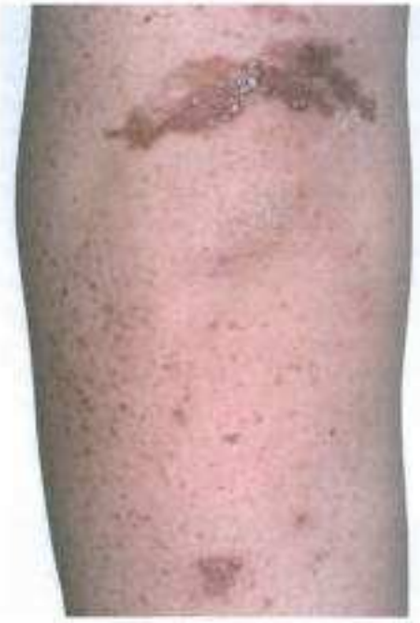


Fig. 20.65 Elastosis perforans serpiginosa. Small, horny, often umbilicated papules occur in an annular or linear arrangement; they ultimately involute to form reticulate atrophic scars. This patient had Down's syndrome. (Courtesy of the late Dr Anil Kagalwala.)

Distribution
The lesions are most common on the legs (Fig. 20.64) and forearms and occasionally the palms, soles and mouth.

Histopathology
There is an adherent, laminated hyperkeratosis with thinning of the malphigian layer and flattening of the rete ridges with a lichenoid infiltrate in the upper dermis. In later lesions, there is a depression and penetration of the keratinous plug, which may provoke a foreign body reaction.

Management
A skin biopsy is helpful for the diagnosis. There is no specific treatment, although retinoids and PUVA have been tried.

ELASTOSIS PERFORANS SERPIGINOSA
An extrusion of elastic fibres through the epidermis.

Aetiology
It begins in early adult life and is four times more common in females. A third are associated with genetic disorders, e.g. Down's, Ehlers–Danlos, osteogenesis imperfecta, Marfan's, pseudoxanthoma elasticum and acrogeria. The primary defect appears to be in the elastic tissue; the epidermis grows downwards to engulf this elastotic material and subsequently extrude it. A similar phenomenon occurs in animals that are copper deficient or given lathyrogens and in patients taking penicillamine, which disrupts desmosome crosslinks within elastin.

Clinical Features
Symptoms
A ringed rash occurs, particularly on the neck or limbs.

Morphology
Small, horny or umbilicated papules occur in linear or annular arrangements (Fig. 20.65), producing a serpiginous pattern; the papules eventually involute and produce reticulate atrophic scars.

Distribution
The neck, cheeks, arms and thighs are affected. The distribution may be bilateral, but not in Down's syndrome.

Management
The lesions can be curetted or frozen with liquid nitrogen. Excision tends to result in keloid formation. It may resolve spontaneously.

Porokeratosis
Porokeratosis refers to a characteristic clinical appearance of plaques with raised horny margins surrounding atrophic centres. It is represented by a group of mainly genetic disorders characterized by local or systemic changes in immune function, which permits the clonal proliferation of atypical cells, which may become neoplastic. There are five variants:

- **Classic (Mibelli)** It is rare, begins in childhood as a small, horny papule, which gradually extends to form a plaque of various shapes (Fig. 20.66). The peripheral part of the plaque is slightly raised and horny.

Fig. 20.66 Porokeratosis of Mibelli. There is an annular plaque with a raised horny rim and central area of atrophy.

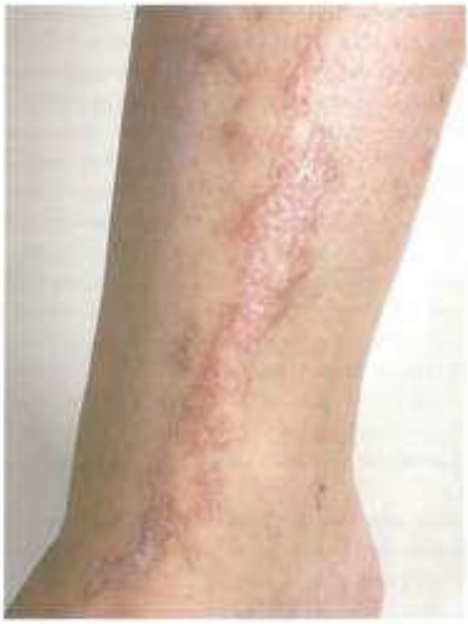


Fig. 20.67 Linear porokeratosis. The eruption consists of papules and plaques with an atrophic centre and horny rim.

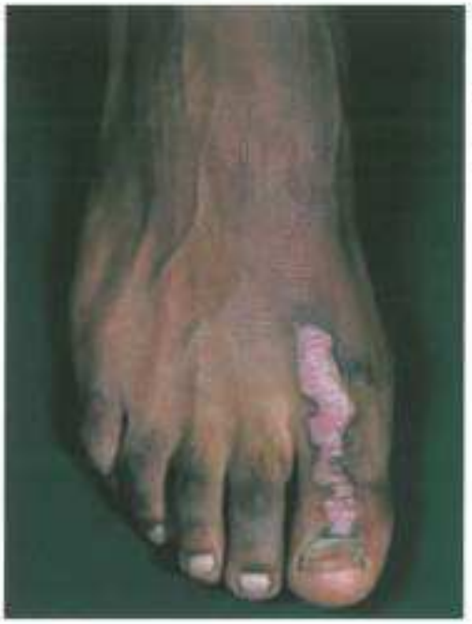


Fig. 20.68 Linear porokeratosis. There is a raised pigmented rim to a pink atrophic linear plaque, which involves the large toenail.

but the central area is atrophic. It may occur anywhere (including mucous membranes), but usually on the extremities.

- **Linear** An autosomal dominant condition presenting in childhood with hyperkeratotic papular and annular plaques with central atrophy and raised borders along the lines of Blaschko (Fig. 20.67), sometimes with nail dystrophy (Fig. 20.68), which may develop into basal or squamous cell carcinoma.
- **Disseminated superficial actinic porokeratosis** (see below).
- **Punctate** 1–2 mm keratotic papules on the palms and soles.
- **Palmaris et plantaris disseminata** This is a rare variant of the above.

Increased p53 protein expression is found in porokeratosis, and it is best regarded as an opportunistic low-grade neoplasm. It can develop in the immunosuppressed, particularly those who have had organ transplantation (Fig. 20.69) or have AIDS.

A skin biopsy is helpful. The hallmark is the *cornoid lamella*, a column of parakeratosis located above a dip in the surface of the epidermis below which there is loss or diminution of the granular cell layer (Fig. 20.70). The cells in the spinous layer may be dyskeratotic or have perinuclear vacuoles. There are often dilated capillaries and a lymphohistiocytic infiltrate in the papillary dermis.

There is no specific treatment, although topical 5-fluorouracil, imiquimod, photodynamic therapy, cryotherapy or retinoids may be effective. There is a risk of the development of squamous cell or basal cell carcinoma.

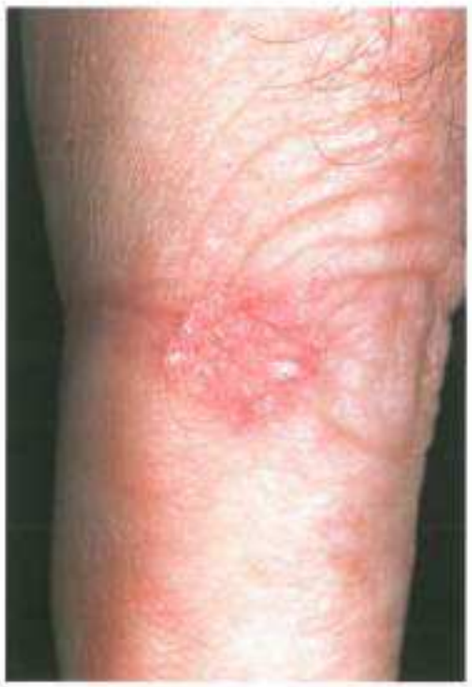


Fig. 20.69 Porokeratosis and organ transplantation. This patient had had a liver transplant. The rim of the atrophic red plaque is pronounced and round. Lesions may be multiple in the immunosuppressed.

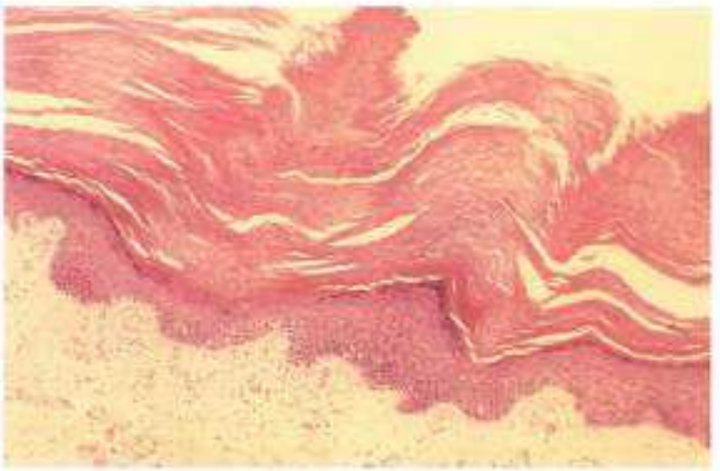


Fig. 20.70 Porokeratosis of Mibelli. The hallmark for diagnosis is a cornoid lamella, which is a column of parakeratosis above a dip in the epidermis that has an absent or diminished granular cell layer.

Epidermolysis bullosa

This is a collection of inherited blistering disorders of the skin characterized by increased skin fragility in response to relatively trivial trauma. In the past, a clinical diagnosis was made on the basis of whether the eruption was localized or generalized, whether it healed with or without scarring, milia formation or hyperkeratosis, and whether there was involvement of the mucous membranes, hair, teeth and nails.

With light microscopy, the epidermal basement membrane is stained pink by periodic acid–Schiff's stain (PAS), but a variety of structures that stretch away from this zone are also always stained. Using the electron microscope, it can be seen that the epidermal basement membrane consists of three distinct layers (Fig. 20.71). The lamina lucida is immediately below the basal plasma membrane in the basal epidermal cells and, in particular, the keratinocytes and melanocytes. It is relatively electron lucent, but very fine anchoring filaments traverse the zone perpendicularly to the plasma membrane. Below this lies a more electron-dense layer known as the lamina densa, the main component of which is type IV collagen (Fig. 20.72). Underneath on the dermal side of the epidermal basement membrane is the sublamina densa fibrillar zone (or reticular layer). Anchoring fibrils are present in this area as well as other structures, including fine type III collagen fibrils. Anchoring fibrils are short, curved structures that fan out at each end, one part inserting into the lamina densa and the other part ending in the papillary dermis or looping around and back into the lamina densa. Anchoring fibrils contain type VII collagen.

Hemidesmosomes occur along the basal surfaces of keratinocytes and attach them to the basement membrane. They have an intracellular and extracellular component. The former is a discrete electron-dense disc that is in contact with the basal plasma membrane. Tonofilaments insert into this part of the hemidesmosome. The sub-basal dense plate is the extracellular component, which is just outside the basal cell within the lamina lucida and parallel to the attachment plaque. Anchoring filaments are more numerous in this area.

There are three phenotypes, which result from different mutations in genes encoding for the protein components of the basement membrane zone. These (with their mutations) are:

- intraepidermal (epidermolytic)
  - simplex (keratin 5 or 14)
  - simplex with muscular dystrophy (plectin)
- intralamina lucida
  - junctional (Herlitz) (laminin 332)
  - junctional (non-Herlitz) (laminin 332 or type XVII collagen)
  - junctional with pyloric atresia ($\alpha_6\beta_4$-integrin)
- sublamina densa (dermolytic)
  - dystrophic (type VII collagen)

Scarring and milia occur in the dystrophic (both dominant and recessive) forms, which distinguishes them from the others, where they only occur after infection. The precise diagnosis is made by using a combination of histopathology, electron microscopy (although there are very few proficient laboratories) and monoclonal antibodies to allow the inherited blistering disorders (Fig. 20.73) to be distinguished from the acquired forms (Fig. 20.74).

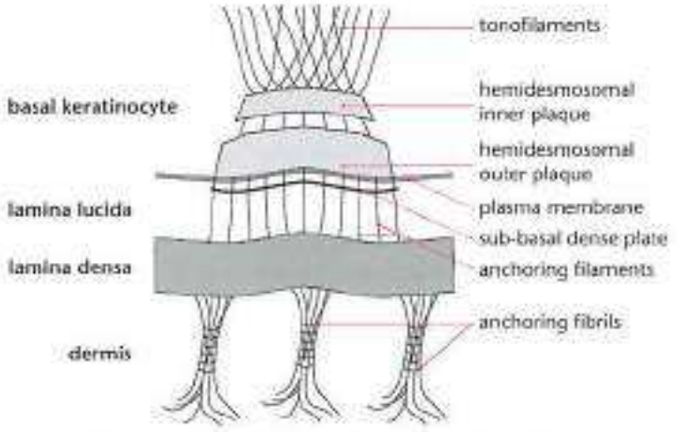


Fig. 20.71 Epidermolysis bullosa. The diagram shows the epidermal basement membrane zone. (Courtesy of Professor John McGrath, Institute of Dermatology.)

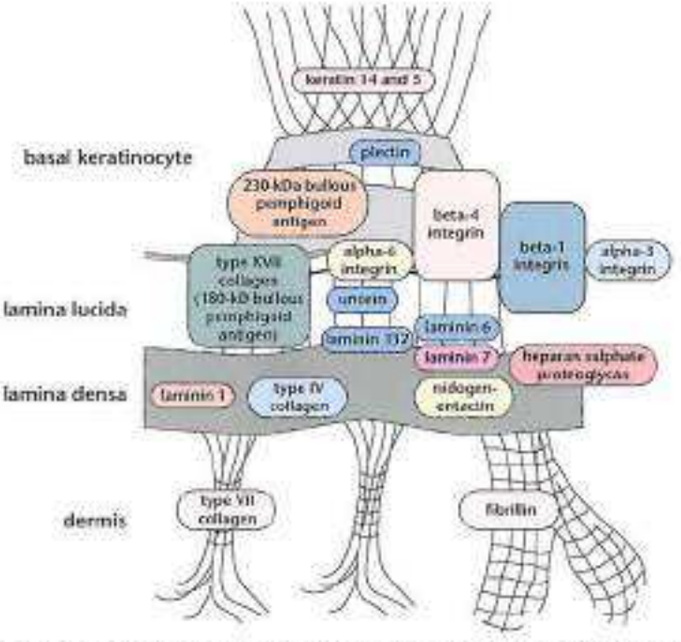


Fig. 20.72 Epidermolysis bullosa. The diagram shows the important structures involved in the pathogenesis of the various forms of epidermolysis bullosa. (Courtesy of Professor John McGrath, Institute of Dermatology.)

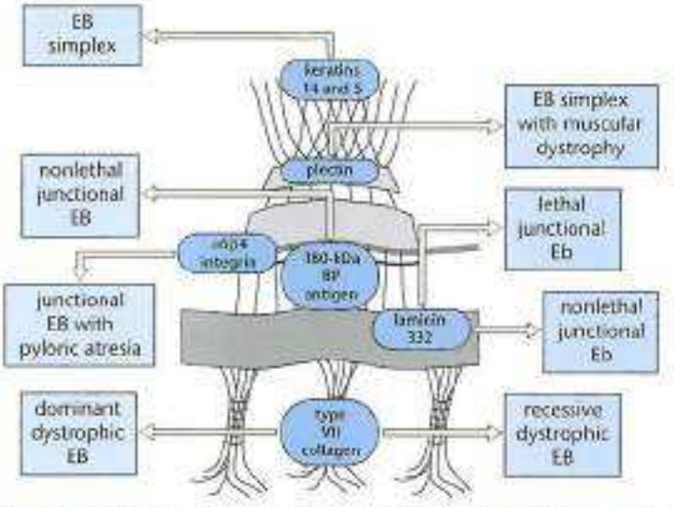


Fig. 20.73 Epidermolysis bullosa. The diagram shows the sites of involvement of the various subtypes of epidermolysis bullosa. (Courtesy of Professor John McGrath, Institute of Dermatology.)

The advantage of electron microscopy is that it permits visualization and semiquantitative assessment of specific structures such as keratin filaments, desmosomes, hemidesmosomes, lamina densa, anchoring filaments and fibrils. Immunofluorescent mapping uses specific monoclonal antibodies to determine the level of split (BP antigen, laminin-1, type IV collagen and keratin 14) and the structures involved (laminin 332, type VII collagen, type XVII collagen, plectin, $\alpha_6\beta_4$-integrin and keratin 14). Mutational analysis is a research tool which is the recommended technique for prenatal and preimplantation diagnosis.

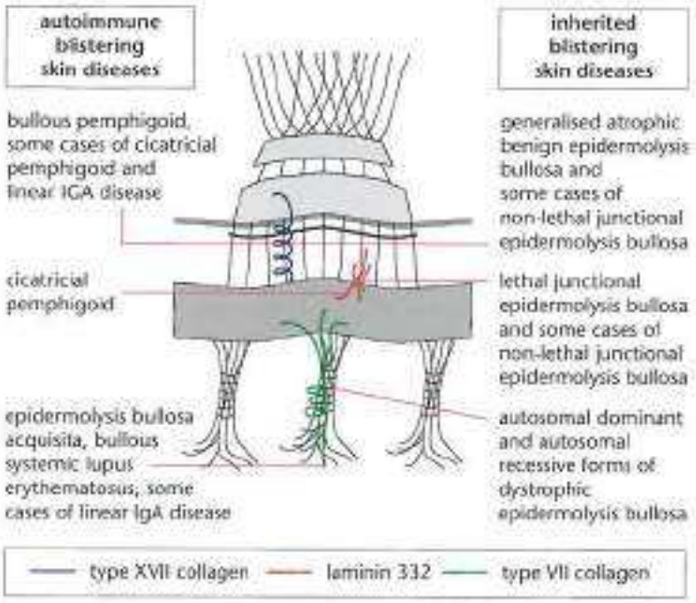


Fig. 20.74 Epidermolysis bullosa. A diagram delineating the differences between autoimmune and inherited blistering disorders. (Courtesy of Professor John McGrath, Institute of Dermatology.)

EPIDERMOLYSIS BULLOSA SIMPLEX

A hereditary disorder of basal cell cytolysis resulting in blisters in response to trauma.

Aetiology

There are four varieties. The first three are autosomal dominant:

- the *Weber–Cockayne variant* is localized mainly on the hands and feet.
- the *Koebner variant* has widespread fragility.
- the *Dowling–Meara variant* is more severe, with generalized arcuate herpetiform blistering associated with nail loss, milia formation and hyperkeratosis of the palms and soles. The blistering decreases with time and the nails do regrow.
- *epidermolysis bullosa simplex with muscular dystrophy*, is inherited as an autosomal recessive; the blistering occurs from birth onwards but progressive muscular dystrophy occurs any time from infancy to adult life and may be fatal.

Epidermolysis bullosa simplex is caused by mutations affecting the genes encoding the basal keratins 5 (*KRT5*) and 14 (*KRT14*); as a result, the tonofilaments fail to maintain cytoskeletal integrity in response to trauma. The mutations are mostly missense changes that lead to dominant negative interference between mutant and wild-type keratin 5 and keratin 14 partners. This results in instability of the keratin intermediate filament network and thereby to fragility of the basal keratinocyte. Dowling–Meara is more severe than Weber–Cockayne, because it is caused by mutations affecting the boundaries of central helical rod domain of K5 and K14 and complete collapse of the cytoskeleton occurs. Mutations in the central part of the keratin molecule (Weber–Cockayne) permit filament assembly albeit that they are structurally weak. In epidermolysis bullosa simplex with muscular dystrophy, there is a mutation in the gene encoding plectin, which is found on the inner plaque of the hemidesmosomes in skeletal muscle and in airway epithelia.

Clinical Features

Symptoms

Blisters present either at birth or shortly afterwards (Fig. 20.75) and may be itchy.

Morphology

Blisters (Fig. 20.76) become erosions and heal, usually without scarring. The severity varies and depends on the intensity of the trauma.

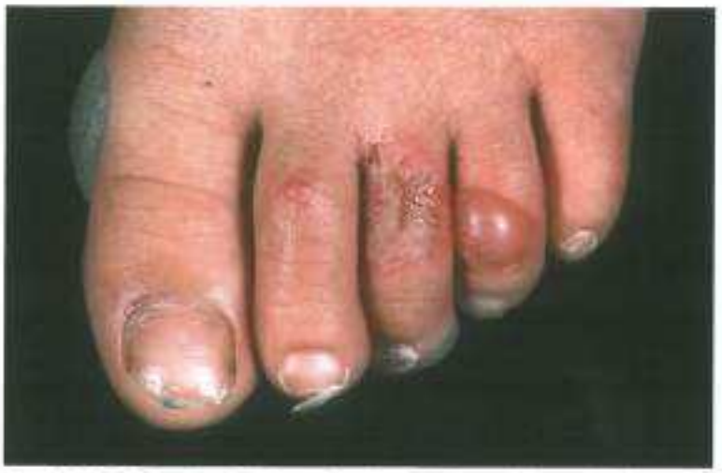


Fig. 20.75 Epidermolysis bullosa simplex. The blisters begin early in life and are confined in straightforward cases to the hands and feet.

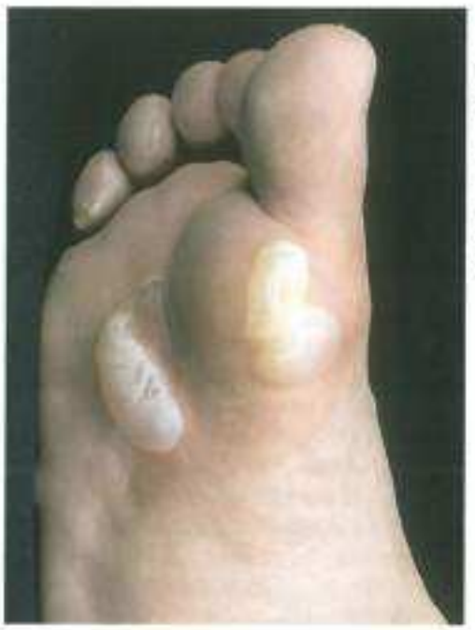


Fig. 20.76 Epidermolysis bullosa simplex. Tense blisters form as a result of trauma; they become eroded and heal without scarring. There may be hyperhidrosis and some hyperkeratosis. (Courtesy of the Institute of Dermatology.)

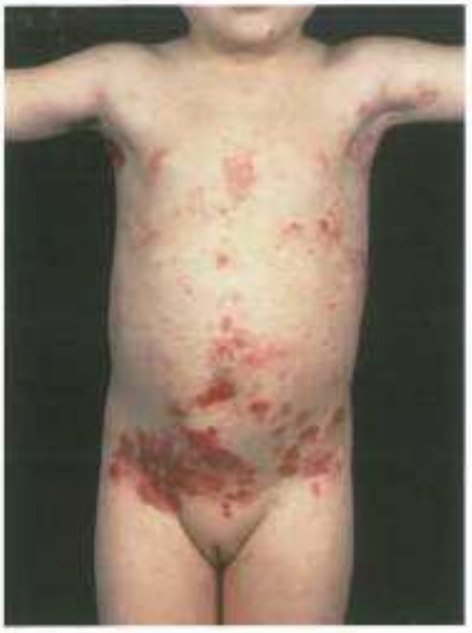


Fig. 20.77 Dowling–Meara epidermolysis bullosa simplex. The appearance of generalized herpetiform blistering with loss of the nails, milia formation and hyperkeratosis of the palms and soles is very characteristic.

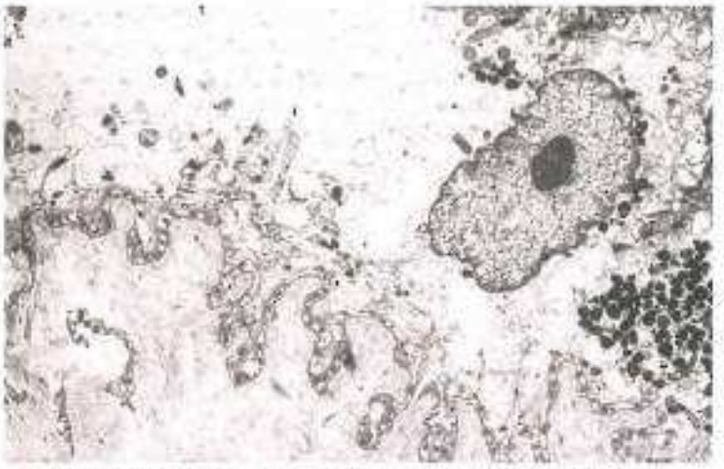


Fig. 20.78 Epidermolysis bullosa simplex. The blisters are intraepidermal (epidermolytic); ultrastructurally, the cleavage is through the basal epidermal cells just above the dermo-epidermal junction. (Courtesy of Professor Robin Eady.)

Distribution

The Weber–Cockayne form occurs on the palms and soles and is associated with hyperhidrosis and often moderate hyperkeratosis. Secondary infection is quite common. The condition improves at puberty, particularly in females. The disorder is exacerbated by warmth and sunshine. More generalized varieties (Koebner and Dowling-Meara) occur (Fig. 20.77). The teeth and hair are spared unlike junctional epidermolysis bullosa.

Histopathology

The disorder is epidermolytic with basal cell cytolysis, which results in marked vacuolation of the basal cell layers of the epidermis. The split occurs, therefore, above the basal lamina.

Diagnosis

The diagnosis can be made clinically, but light microscopy is usually sufficient to substantiate the diagnosis. Electron micrographs show the cleavage through the basal epidermal cells just above the dermo-epidermal junction (Fig. 20.78) and clumping of the tonofilaments. Immunofluorescent mapping techniques are definitive. Botulinum has been used therapeutically.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

A severe, autosomal recessive, generalized, blistering of the skin and mucous membranes, with a tendency to scarring, caused by an abnormality of the hemidesmosome anchoring filament complex, resulting in blistering within the lamina lucida.

Aetiology

Herlitz first described it as *epidermolysis bullosa lethalis*. However, some patients with identical histological characteristics but different clinical features survive for long periods. Junctional epidermolysis bullosa is now subdivided into Herlitz and non-Herlitz types. In both there is reduced or absent expression of laminin 332, which is the major component of the anchoring filaments. This protein is a heterotrimer of three polypeptide chains (α_3, β_3 and γ_2), each of which is encoded by a gene: *LAMA3*, *LAMB3* and *LAMC2*, respectively. Mutations on one or more of these genes cause junctional epidermolysis bullosa. *Generalized atrophic benign epidermolysis bullosa* (now known as the non-Herlitz type) is caused by a mutation in the gene encoding the β_3-subunit of laminin 332, which is also the target antigen of 180 kDa bullous pemphigoid antigen, also known as type XVII collagen (*COL17A1*).

Rare variants are:

- *Junctional epidermolysis bullosa with pyloric atresia*. There is severe mucocutaneous fragility and gastrointestinal atresia, which leads to failure to thrive and is usually fatal. There is a mutation in the gene encoding for the hemidesmosomal $\alpha_6\beta_4$-integrin.
- *Shabbir's syndrome* (laryngo-onycho-cutaneous syndrome). It has similar clinical features to junctional epidermolysis bullosa but is due to a mutation in α_3 chain of laminin 332.

Revertant mosaicism has been described, whereby complete or partial rescue of the pathogenic mutation occurs via somatic gene conversion, i.e. the normal region of one allele converts the mutated region of the other allele to the wild type sequence, so the patient reverts to normal areas of skin where type VII collagen was patchily expressed.

Clinical Features

Symptoms

Generalized blistering occurs.

Morphology

The blisters result in erosions that heal slowly with atrophy, but without scarring or milia formation unless complicated by secondary infection.

Distribution

The blisters are generalized (Fig. 20.79) although the hands and feet are usually spared. The nails are repeatedly lost, ultimately permanently. There are often vegetating lesions, particularly around the mouth. Oral involvement is severe and the oesophagus may be affected. The teeth are abnormal since junctional disorders involve the dental enamel and lead to caries.

In the non-Herlitz type (Fig. 20.80), similar blistering occurs, which heal with cigarette paper-like atrophy (Fig. 20.81), hyper- and hypopigmentation but without milia formation. In this form, the lesions are widespread, particularly on the extremities but also on the face, trunk and scalp. There is significant alopecia not only of the scalp but also the body, including the eyelashes and eyebrows. There is hypoplasia of the dental enamel. The nails are hypoplastic or dystrophic. There is mild involvement of the mucous membranes and there are acquired melanocytic naevi.

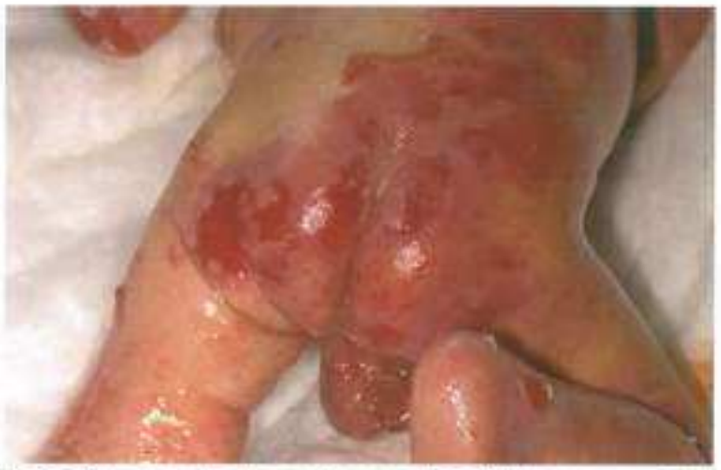


Fig. 20.79 Junctional epidermolysis bullosa. The infant has severe generalized blistering, with erosions that heal without scarring unless complicated by infection. It is often fatal. (Courtesy of Professor Robin Eady.)

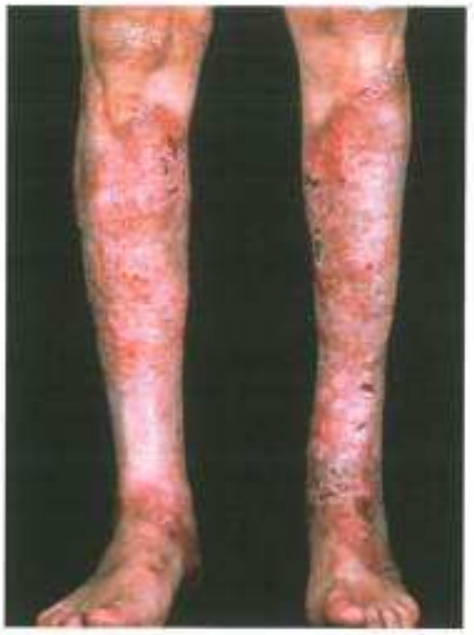


Fig. 20.80 Generalized atrophic benign epidermolysis bullosa. This term is abandoned because it is not benign (squamous cell carcinoma may develop) and the clinical findings overlap with non-Herlitz type junctional epidermolysis bullosa.

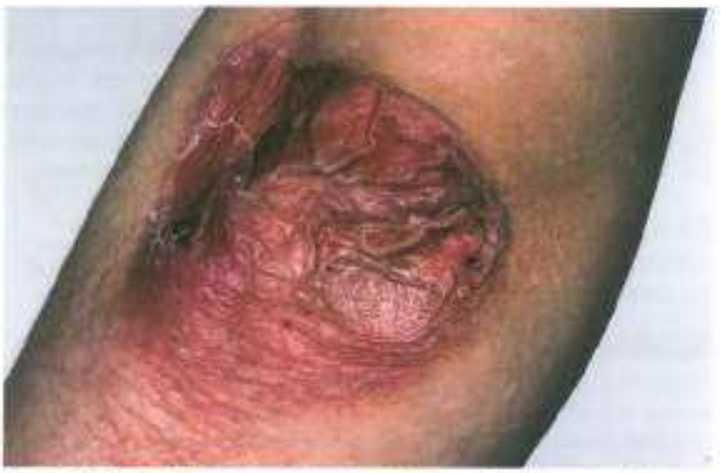


Fig. 20.81 Non-Herlitz type epidermolysis bullosa. The blisters heal with cigarette paper-like atrophy of the skin, but without milia formation.

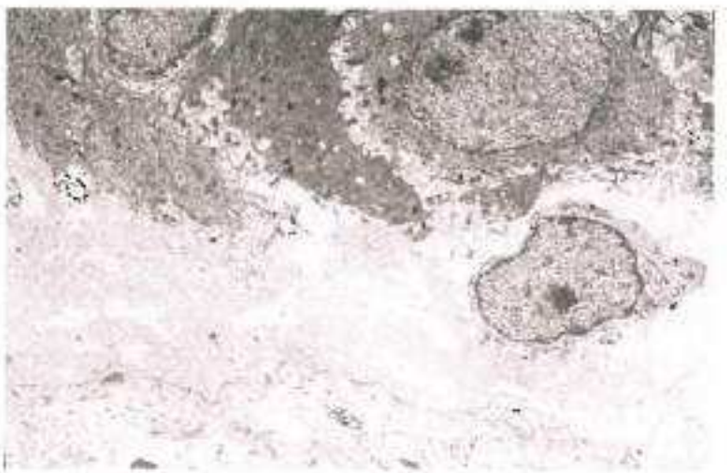


Fig. 20.82 Junctional epidermolysis bullosa. The level of separation is through the lamina lucida of the epidermal basement membrane. The lamina densa remains on the blister floor, and the basal epidermal cells are seen at the roof. (×4800). (Courtesy of Professor Robin Eady.)

Systemic features

Junctional epidermolysis bullosa is commonly fatal but, if patients survive, there is gross mental retardation and severe anaemia. In the non-Herlitz type, the blistering improves with age. Growth is normal, anaemia is rare and the patients survive into adult life. Squamous cell carcinomas, however, may develop, particularly on the extremities and in the mucous membranes.

Histopathology

Light microscopy reveals a subepidermal bulla, which may be shown with electron microscopy to be occurring in the lamina lucida (Fig. 20.82). There are reduced numbers of hemidesmosomes.

DOMINANT DYSTROPHIC EPIDERMOLYSIS BULLOSA

A disorder of fragility, blistering and scarring of the skin with milia formation and nail dystrophy that presents in infancy, caused by a mutation in *COL7A1*, the gene encoding type VII collagen, which is the major component of anchoring fibrils.

Aetiology

It is very rare and inherited as an autosomal dominant. There is a subepidermal blister below the basal lamina. The anchoring fibrils are rudimentary and reduced in localized blister-prone zones in the *Cockayne–Touraine variety* and throughout the skin in the *Pasini variant*. There is

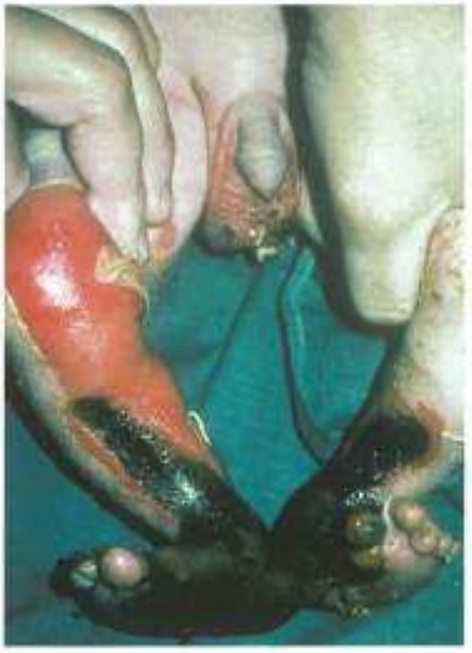


Fig. 20.83 Bart's syndrome. This term refers to a congenital localized absence of the skin and has been abandoned because it may occur in any of the major forms of epidermolysis bullosa.

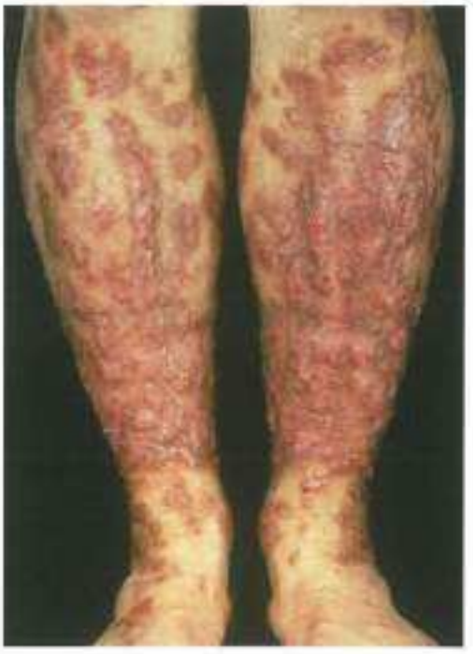


Fig. 20.84 Pretibial epidermolysis bullosa. There are extensive, pruriginous lesions as well as blistering and scarring over the tibia, commencing in adult life. The nails are abnormal. Anchoring fibrils are rudimentary. (Courtesy of Professor Robin Eady).

usually glycine substitution in the collagenous triple helical domain of type VII collagen, causing dominant negative interference with wild-type protein and disruption of anchoring fibril assembly. There are two other rare subtypes:

- **Bart's syndrome** (Fig. 20.83) refers to a congenital localized absence of the skin, affecting particularly the lower extremities, blistering of the skin and/or mucous membranes and absence or deformity of the nails. The gene for the disease has been mapped to chromosome 3p at or near the site of the gene encoding type VII collagen. The condition does get better and is possibly caused by the physical trauma of rubbing the legs together in utero. The term has been eliminated in a recent classification because localized absence of skin may occur in any of the major types of epidermolysis bullosa.
- **Pretibial epidermolysis bullosa (epidermolysis bullosa pruriginosa)** (Fig. 20.84). This has a relatively delayed onset even appearing in adult life. It is particularly pruritic and there are extensive prurigo-like lesions as well as blisters, ulcers and scarring. The nail dystrophy may be the clue to diagnosis. Anchoring fibrils are rudimentary and mutations of *COL7A1* have been demonstrated. Inheritance is variably sporadic, dominant or recessive. Tacrolimus typically may help the pruritus.

Clinical Features

Symptoms

The blistering begins in infancy or early childhood.

Morphology

Blistering leads to milia formation (Fig. 20.85). In the Pasini variant, healing was thought to produce atrophic rather than hypertrophic scarring, and characteristic flesh-coloured, scar-like (*albopapuloid*) lesions (Fig. 20.86) occur on the trunk in skin that has not blistered.

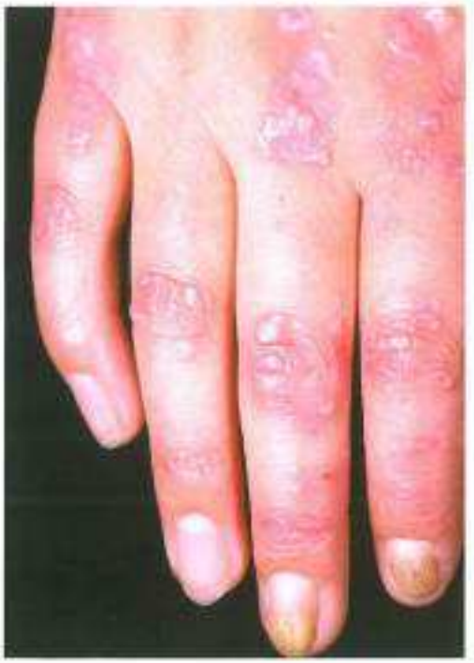


Fig. 20.85 Dominant dystrophic epidermolysis bullosa. Milia (tiny white papules) occur after the blisters have healed. (Courtesy of the Institute of Dermatology.)

Fig. 20.86 Dominant dystrophic epidermolysis bullosa. Rather characteristic but inconsistent flesh-coloured, scar-like plaques (albopapuloid lesions) occur on the trunk. (Courtesy of Professor Robin Eady.)

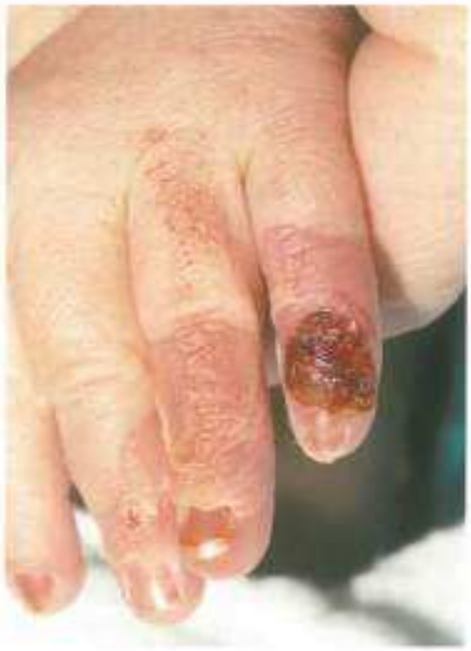


Fig. 20.87
Dominant dystrophic epidermolysis bullosa. In the Cockayne-Touraine variety, the blisters are usually present at birth and tend to be localized to the extremities. Nail dystrophy results.

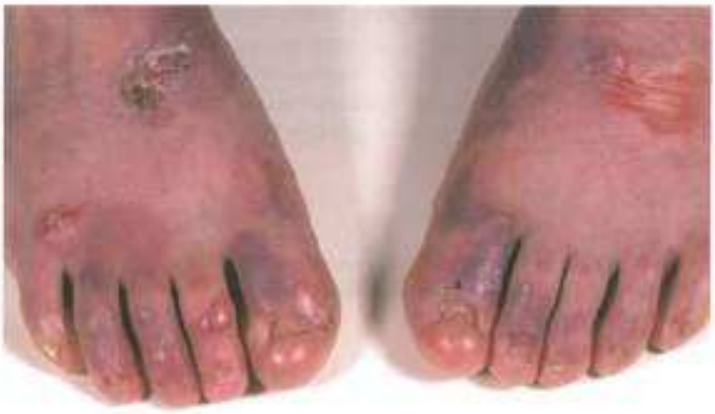


Fig. 20.88 Dominant dystrophic epidermolysis bullosa. Blisters occur mainly on the extremities, induced by trauma. They become eroded and heal with scarring. The nails are therefore dystrophic or absent.

Distribution

In the Cockayne-Touraine variety, the blisters are localized mainly to the extremities (Figs 20.87 and 20.88) but in the Pasini variant are more extensive (Fig. 20.89), although later on become localized to the hands, feet, elbows and knees.

The nails are dystrophic or absent; the teeth, however, are normal and the mouth is infrequently involved.

Histopathology

The blister is subepidermal and milia are identifiable. The basement membrane (stained with PAS) is attached to the roof of the blister. The anchoring fibrils are abnormal and electron microscopy shows the cleavage to be below the lamina densa.

AUTOSOMAL RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

A disorder with a wide clinical spectrum, characterized in severe cases by mucocutaneous blistering, digital fusing (Fig. 20.90), contractions and strictures caused by a loss of anchoring fibrils and marked collagen degeneration in the dermis as a result of abnormally high levels of collagenase, which catalyses the first cleavage in collagen degeneration.

Aetiology

This is a rare autosomal recessive disorder. There is a subepidermal blister below the PAS-stained basement membrane on light microscopy and beneath the lamina densa on electron microscopy; it is associated with marked collagen degeneration in the papillary portion of the dermis. There

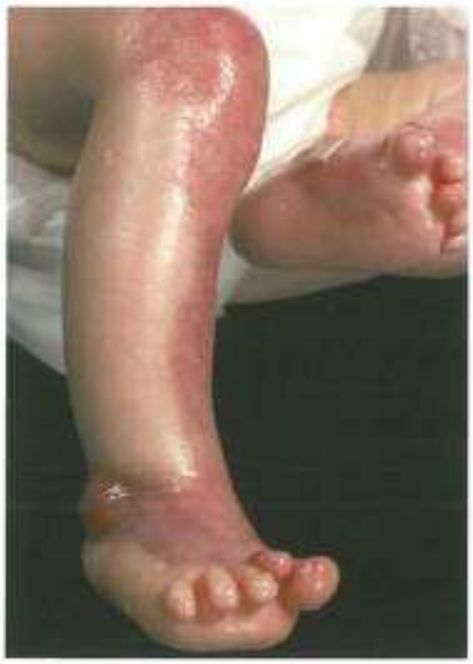


Fig. 20.89
Dominant dystrophic epidermolysis bullosa. In the Pasini variant, the blistering was considered to be more extensive and to heal with atrophic scarring. (Courtesy of Dr David Atherton.)

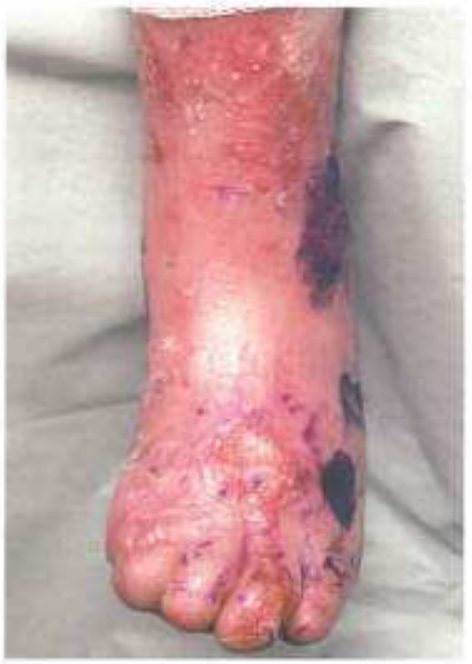


Fig. 20.90
Recessive dystrophic epidermolysis bullosa. The erosions are slow to heal. The scarring which results leads to fusion of the digits. (Courtesy of the Institute of Dermatology.)

are diminished or absent anchoring fibrils, both in involved and non-blistered skin. The condition is caused by complete absence, altered synthesis, abnormal polymerization or excessive breakdown of collagen VIIc molecule. It results from the mutations in the gene *COL7A1*, which encodes the anchoring fibril protein of type VII collagen.

Clinical Features

Symptoms

There is considerable variation in the severity of affliction in subjects with this disorder. It is usually present at birth.

Morphology

There is fragile skin, which leads to blistering, erosions, scarring and mutilation.

Distribution

Some neonates have a relatively localized blistering process, limited largely to the extremities, in particular to the hands, feet, elbows and knees. Others have a much more widespread involvement.

The mucous membranes are involved. Intraoral blistering leads to microstomia and ankyloglossia from the scarring and enamel hypoplasia produces severe dental caries.

The blisters, which are slow to heal, are frequently complicated by atrophic scarring and milia formation, especially around the hands and feet where fibrosis leads to fusion of the digits. Flexural contractures occur at the knee, elbow, wrist and ankle joints.

Systemic features

Mucous membrane involvement, not only of the oral cavity but also of the epithelium of the whole gastrointestinal tract, is common and serious causing difficulties with eating and defaecation. Strictures develop as well as oral, cutaneous (especially at scar sites) and oesophageal carcinomas. Morbidity and mortality are high in this depressing illness. 80% die from metastatic carcinoma by mid-adult life.

Diagnosis

The localized varieties are difficult to distinguish from mild dominant dystrophic epidermolysis bullosa without electron microscopy or immunofluorescent mapping. Prenatal diagnosis is achieved through fetoscopy and skin biopsy. The blister is within the basal lamina. Anchoring fibril remnants are present in the roof and collagenolysis in the upper dermis in the floor of the blister.

Management of Epidermolysis Bullosa

There is no specific treatment for these disorders, although in the past high doses of systemic steroids have been tried and phenytoin has been used in recessive dystrophic epidermolysis bullosa. Patients with the simplex form manage relatively well, especially when they are older and avoid trauma. Tetracyclines and phenytoin have been used for the simplex types, although the efficacy of the latter has not been borne out by double-blind trials. Retinoids have also been used and the pruritus may respond to cyproheptadine.

The junctional dystrophic types require a multidisciplinary approach with special nursing, and early treatment of infection, hand-splinting to prevent contraction and sometimes surgery to release contractions. The use of tissue-engineered skin and acellular dermal allografts, which are structurally intact but have the targets of the immune response (epidermal endothelial cells and fibroblasts) removed, are novel techniques to repair eroded and contracted skin. Ophthalmological supervision and dental care is essential. Attention to nutrition is fundamental, including blood transfusions and iron supplements.

Constipation is common but usually responds to mineral oil. Moisturizers are used routinely on the skin. Secondary infection can be helped with the use of topical mupirocin. Vaseline-impregnated gauzes are used for ulcers and often the dressings need to be changed under general anaesthetic. Perhaps the most important advance in the management of these severe disorders is the use of the fetoscope to perform a skin biopsy in utero if there is a family history and first trimester DNA-based prenatal diagnosis.

Incontinentia pigmenti

Incontinentia pigmenti (*Bloch–Sulzberger syndrome*) is an X-linked, dominantly inherited ectodermal disorder that is usually lethal in males prenatally. It has three cutaneous phases of blisters, verrucous lesions and hyperpigmentation; it is often associated with neurological, ocular and dental disorders in females.

Aetiology

Mutations in the NEMO (nuclear factor kappa B essential modulatory) gene on Xq28 cause the disease. The NEMO protein is a subunit of a kinase which activates NFκB which protects against TNFα-induced apoptosis.

It does very rarely occur in males, probably as a result of post-zygotic mosaicism. It is associated with Kleinfelter's syndrome, and hypohidrotic ectodermal dysplasia with severe immunodeficiency in surviving males.

Clinical Features

Symptoms

A linear perinatal eruption of blisters occurs followed by verrucous and pigmented lesions.

Morphology

There is a wide range of involvement in individuals.

Classically there are three phases. The inflammatory, vesiculo-bullous stage (Fig. 20.91) may persist for several months. Leucocytosis and eosinophilia are usually present. The verrucous stage (Fig. 20.92) begins early, often within the first few weeks. The hyperpigmented stage (Fig. 20.93) begins between the third and sixth months. Bizarre, macular, hyperpigmented lesions may be brown or slate-grey in colour and are distributed in whorls and bands, particularly on the trunk. The pigmentation increases over the next couple of years and then gradually fades, so that it has usually gone by adolescence or early adult life. Some patients have depigmentation rather than hyperpigmentation. Occasionally, the first two stages are not seen and only the pigmentation is present; this is possibly because the blistering and verrucous stages have already taken place in utero. There is a rare fourth stage that begins in puberty and persists. It comprises pale, hairless, hypohidrotic patches of atrophic skin, which is most obvious on the posterior calves.

Distribution

Usually occurs along a limb or on the trunk in a linear manner corresponding to Blaschko's lines. A scarring alopecia and nail changes (onycholysis, ridging, pitting and subungual necrotic tumours) are occasionally found.

Systemic features

There are many associated anomalies. The most common are dental (partial anodontia, late dentition and malformed teeth). Of the ocular changes, squint is the most common, but also cataracts, microphthalmia, optic atrophy, retinal detachment and blindness. Central nervous system abnormalities occur in a third. Mental retardation and spastic paralysis

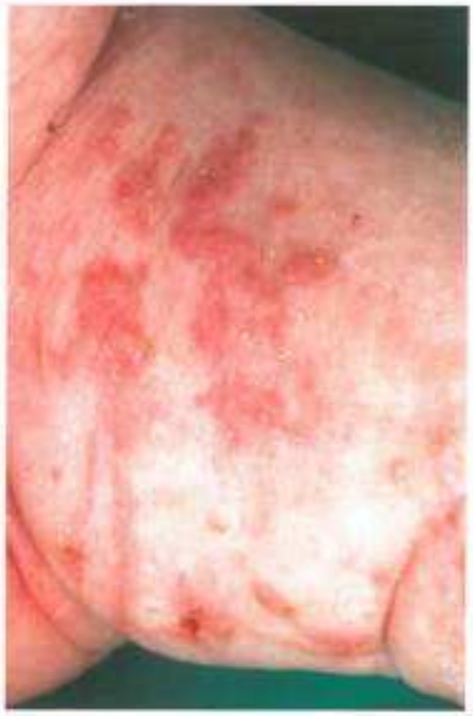


Fig. 20.91
Incontinentia pigmenti. In the first stage, there are vesicles that coalesce, often distributed in a linear manner on a limb. Leucocytosis and eosinophilia are usually present.

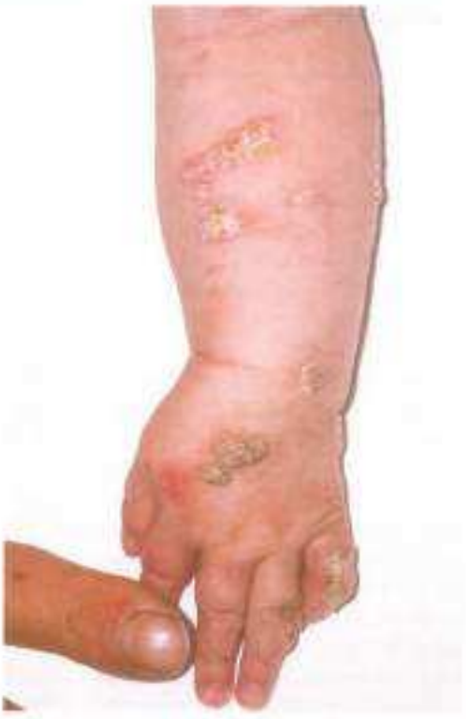


Fig. 20.92
Incontinentia pigmenti. The lesions become verrucous within a few weeks. Only females are affected since it is lethal in males. (Courtesy of Dr David Atherton.)

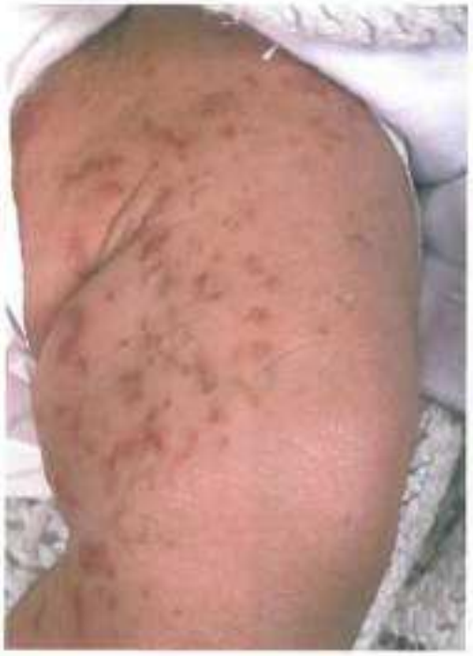


Fig. 20.93
Incontinentia pigmenti. Linear areas of hyperpigmentation develop after the third month and there are many associated anomalies, including of the central nervous system. (Courtesy of Dr David Atherton.)

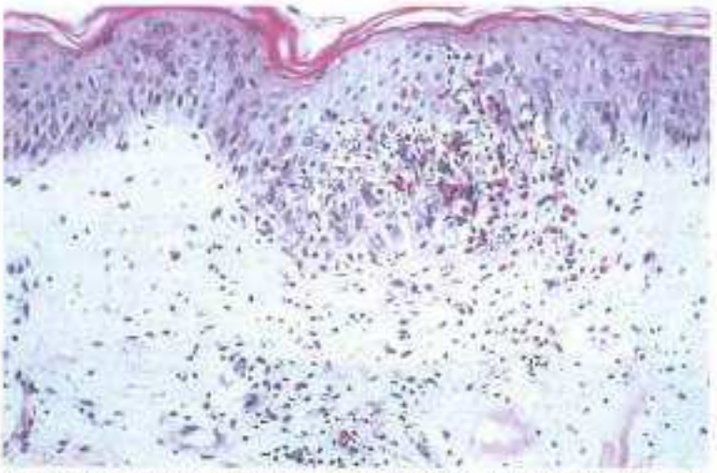


Fig. 20.94 Incontinentia pigmenti. The epidermis shows intense spongiosis, an intense eosinophil infiltrate and clusters of dyskeratotic keratinocytes.

occur in about 10%. Convulsions and microcephaly may occur. There is a variable dysfunction of the immune system but the disorder rarely causes serious infection. There is an increased instance of childhood malignancy, particularly retinoblastoma, Wilms' tumour, acute myeloid leukaemia and rhabdomyosarcoma.

Histopathology

In the vesiculo-bullous phase there is an eosinophilic spongiosis (Fig. 20.94) with vesicle formation, clusters of intraepidermal dyskeratotic keratinocytes and a dermal infiltrate of eosinophils and mononuclear cells. This is virtually diagnostic. In the verrucous phase, there are mononuclear cells in the dermis, epidermal hyperplasia and hyperkeratosis, with scattered dyskeratotic cells in the epidermis. In the pigmentary phase, there is pigmentary incontinence and dermal melanophages.

Management

The diagnosis can usually be easily established from the clinical picture and confirmed with a skin biopsy. There is no specific treatment.

Developmental disorders associated with pigmented macules

Café-au-lait macules (CALMS), when they occur in significant numbers, are a feature of:

- **Neurofibromatosis type 1** (Fig. 20.95)
- **McCune–Albright's syndrome** a disorder of polyostotic fibrous dysplasia, endocrine dysfunction and precocious puberty in females. It may be difficult to distinguish from neurofibromatosis in early life, although in Albright's syndrome the macules are unilateral (either segmental or linear), fewer, larger, darker and have more jagged borders (Fig. 20.96). They tend to occur on the forehead, neck, sacrum and buttocks. Giant pigment granules (melanin macroglobules) are found in dopa-incubated split skin preparations in neurofibromatosis, but not in Albright's syndrome. The McCune–Albright's syndrome is an example of somatic mosaicism, that is there is postzygotic mutation after fertilization and, therefore, only a proportion of the cells are affected. The bony abnormalities usually occur on the same side as the skin involvement, which is almost always unilateral along Blaschko's lines since the precursor cells are already committed to one side of the integument. It is not transmissible. If the gonads are affected, the mutation is lethal at conception. The disorder is only tolerated in a mosaic state.
- **Watson's syndrome** which comprises pulmonary stenosis, mental deficiency, café-au-lait macules and axillary and perineal freckling. Molecular linkage studies suggest that Watson's syndrome is allelic to neurofibromatosis type 1, or that there are contiguous genes on 17q; consequently, it is probably not surprising that café-au-lait macules are seen with a similar frequency in Watson's syndrome as in neurofibromatosis.
- **Ring chromosome syndrome** which is a phenotype of microcephaly, mental retardation, short stature and skeletal abnormalities. Chromosomes 7, 11, 12 and 15 may be involved.
- **Bloom's syndrome** (see below).
- **Fanconi's anaemia** (see below).

Freckles or ephelides are small macules that are extremely common in fair-skinned individuals in early childhood on light-exposed areas such as the face. They are most prominent in the summer and tend to fade in the winter. They result from increased melanin production. Freckle-like macules occur in neurofibromatosis, particularly in non-exposed areas such as the axillae and perineum.

Lentigines are the result of an increase in the number of melanocytes. Syndromes associated with multiple lentigines include:

- **The Carney complex** This is an autosomal dominant endocrinopathy (Cushing's syndrome due to primary pigmented nodular adrenocortical disease) with neoplasia (cardiac myxoma, myxoid mammary fibrodenoma, cutaneous or mucosal myxomas and blue naevi) and lentigines (of the lips, conjunctivae, inner and outer canthi and genital mucosa). It is caused by a mutation on chromosome 2p16 and 17q22-24, which encodes the regulatory subunit RIA of protein kinase. Sporadic cases have been called NAME (naevi, atrial myxoma, myxoid neurofibromata and ephelides) (Fig. 20.97) and LAMB (lentigines associated with atrial myxoma, mucocutaneous myxomas and blue naevi).
- **LEOPARD** (lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and deafness) *and Noonan syndrome*. These are linked to mutations in *PTPN11*, a gene on chromosome 12q24, which encodes non-receptor tyrosinase protein tyrosinase phosphatase Shp-2. It is occasionally associated with neurofibromatosis and Noonan syndrome. The lentigines in Leopard syndrome are similar to those of Carney complex, but more profuse. *Moynahan's syndrome*, a disorder of genital hypoplasia, growth and mental retardation, is probably a variant of the Leopard syndrome.
- **Noonan syndrome** An autosomal dominant is characterized by developmental delay, dyslexia, low posterior hair loss, coarse curly hair, pulmonary stenosis, skeletal (including short stature) and testicular abnormalities, lymphoedema and multiple naevi (Fig. 20.98).
- **Peutz–Jeghers syndrome** (see below).

Generalized increase in skin pigmentation coupled with ephelides and large, hyperpigmented café-au-lait patches occur in *Fanconi's anaemia*. This is an autosomal recessive disorder characterized by congenital malformations of the skeletal, ophthalmic, urogenital, central nervous and gastrointestinal systems, which may progress to bone marrow failure and malignancy. It is characterized by spontaneous chromosomal breaks and hypersensitivity to DNA cross-linking agents such as mitomycin C.

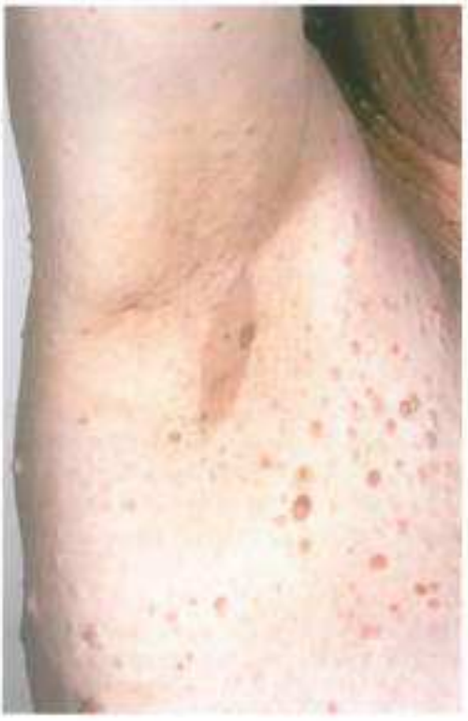


Fig. 20.95 Café-au-lait patches. These are not uncommon but in association with axillary freckling they are pathognomonic of neurofibromatosis.

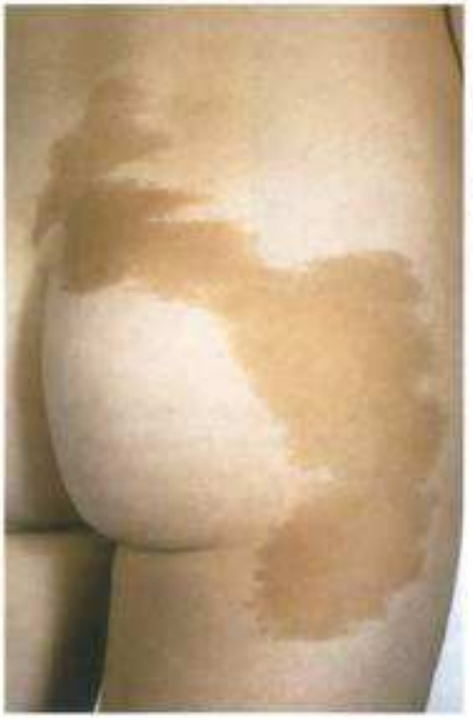


Fig. 20.96 The McCune–Albright's syndrome. The café-au-lait macules are fewer, larger, darker and have more jagged borders than those of neurofibromatosis. They are almost always unilateral. (Courtesy of Dr David Atherton.)

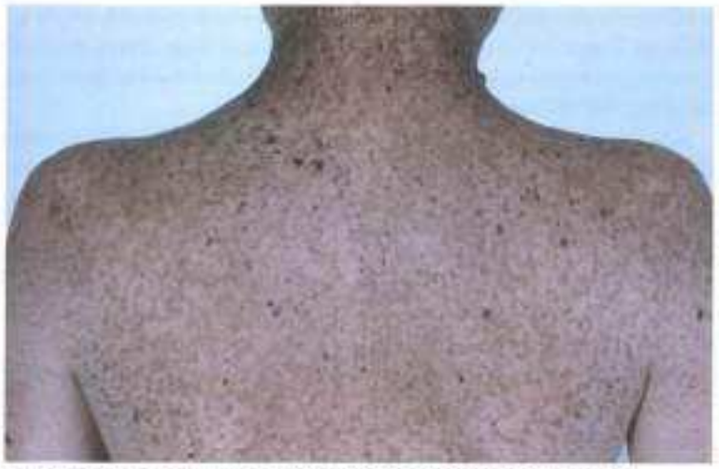


Fig. 20.97 NAME syndrome. Multiple freckles are associated with atrial myxoma, myxoid neurofibromas and naevi. (Courtesy of Dr David Atherton.)

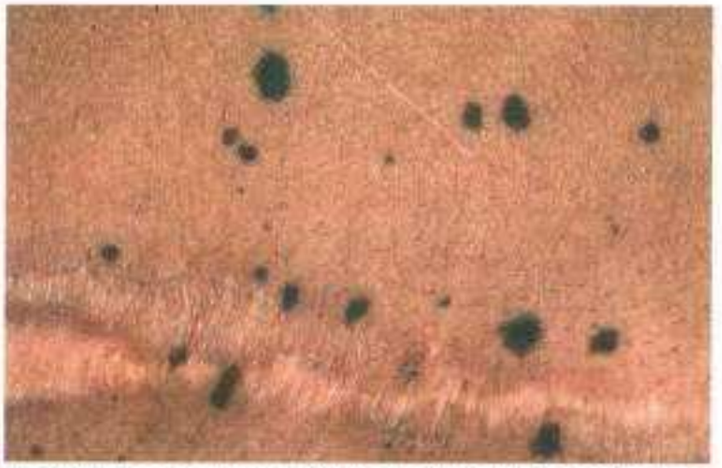


Fig. 20.98 Noonan's syndrome. Multiple quite striking naevi are associated with this autosomal dominant disorder. Cardiac (especially pulmonary valve stenosis), skeletal and testicular defects are common.

PEUTZ–JEGHERS SYNDROME

A syndrome of pigmented macules of the mouth and extremities, associated with gastrointestinal polyps.

Aetiology

It occurs in both sexes and all races. It is inherited as an autosomal dominant although 40% of cases are new mutations. It is due to a mutation in the serine/threonine kinase-encoding gene *LKB1/STK11*. It has variable manifestations and may be monosymptomatic. Clinically normal carriers occur.

Clinical Features

Symptoms

Freckles occur on the face, lips, in the mouth and on the hands and feet.

Morphology

There are round or oval macules 1–5 mm in diameter, which may be brown, black or tan in colour, at birth or in early childhood.

Distribution

The macules occur in profusion around the lips, especially the lower, and on the buccal mucosa (Fig. 20.99), gums, hard palate, face, hands (Fig. 20.100) and feet. Clubbing may occur.

Systemic features

It is associated with polyps of the gastrointestinal tract, particularly the small bowel. This may give rise to abdominal pain, bleeding and occasionally intussusception. Rarely, these polyps are premalignant.

Management

The localization of the pigmented macules around and within the mouth and on acral areas serves to distinguish it from Carney's syndrome, where lentigines are also profuse, but intraoral pigmentation is less common and conjunctival more so. Gastrointestinal polyposis and diffuse pigmentation occurs in the *Cronkhite–Canada syndrome*, but the mucous membranes are spared, although the hands and fingers are involved and alopecia and nail dystrophy also occur. Biopsy of a pigmented macule shows an increase in the melanocytes in the basal layer and an increase in pigment-laden macrophages in the upper dermis. The patient should be managed with regular colonoscopy. A minority of female patients also have ovarian tumours.

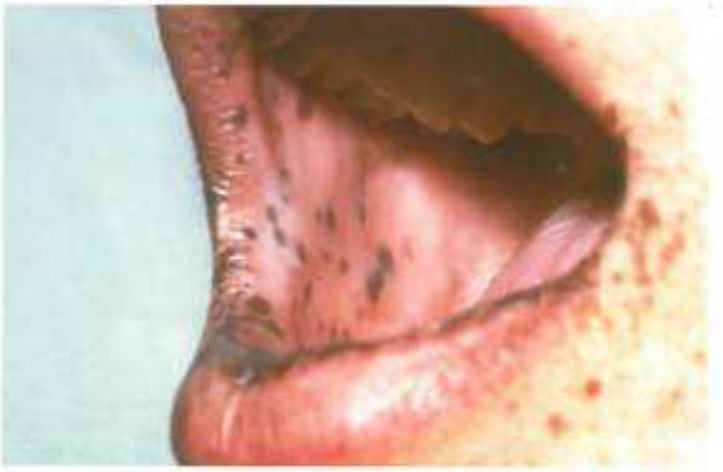


Fig. 20.99 Peutz–Jeghers syndrome. Brown pigmented macules on the buccal mucosae and lips (especially lower) are associated with polyposis of the gastrointestinal tract. (Courtesy of Dr B. Leppard.)

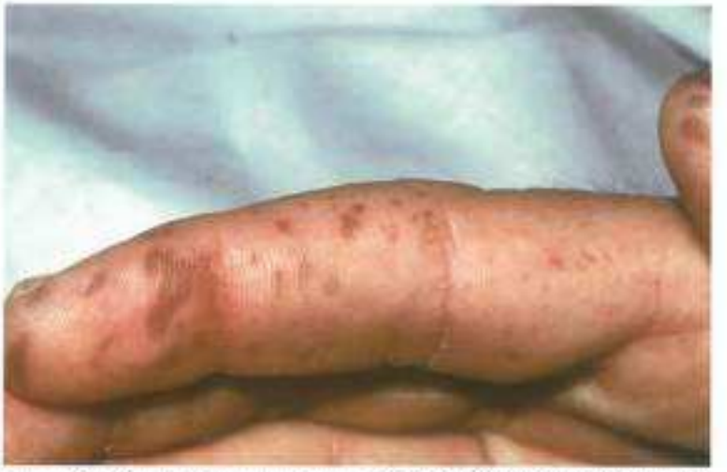


Fig. 20.100 Peutz–Jeghers syndrome. The condition is associated with polyps of the gastrointestinal tract (particularly the duodenum). It is inherited as an autosomal dominant. (Courtesy of Dr B. Leppard.)

NEUROFIBROMATOSIS

A variety of neurocutaneous syndrome associated with café-au-lait macules, axillary and perineal freckling, Lisch nodules, neurofibromas and other abnormalities.

Aetiology

Neurofibromatosis (*Von Recklinghausen's disease*) is dominantly inherited, occurring in approximately 1 in 3000 births, although half are spontaneous mutations. There are several different types. Type 1 is linked to the gene *NF-1*, which is localized to chromosome 17q 11.2 and encodes a tumour suppressor factor. It is a huge gene, which probably explains the high frequency of new mutations. It produces neurofibrin. Juvenile xanthogranulomas may be associated with *NF-1* in males and there is an increased risk of juvenile chronic myeloid leukaemia.

Type 2 (central) neurofibromatosis is characterized by bilateral acoustic neuromas, which are usually present before 20 years of age but develop eventually in all patients. Only 60% have café-au-lait patches, which are larger, paler and fewer (greater than five is unusual), and flexural freckling and plexiform neuromas are rare. A unique skin lesion is a superficial well-demarcated papule with a rough and hypertrichotic surface, a schwannoma. Sarcomatous change does not occur and Lisch nodules are rare. The gene is present on 22q11-q13. It encodes merlin, which coordinates cellular adhesion and growth factor receptor response. 50% represent a new mutation.

Type 3 is a mixed form and type 4 is a variant with café-au-lait macules and neurofibromas presenting diffusely. Type 5 is a segmental form. There are café-au-lait macules and/or neurofibromas occurring in a limited portion of the body; type 5, therefore, represents a somatic mutation of *NF-1*. Genetic transmission may occur in offspring. Type 6 neurofibromatosis may be familial or sporadic. There are multiple, diffuse café-au-lait macules but no other cutaneous or systemic expression of *NF-1*. Type 7 is late onset and type 8 is not yet classified but does not involve café-au-lait macules.

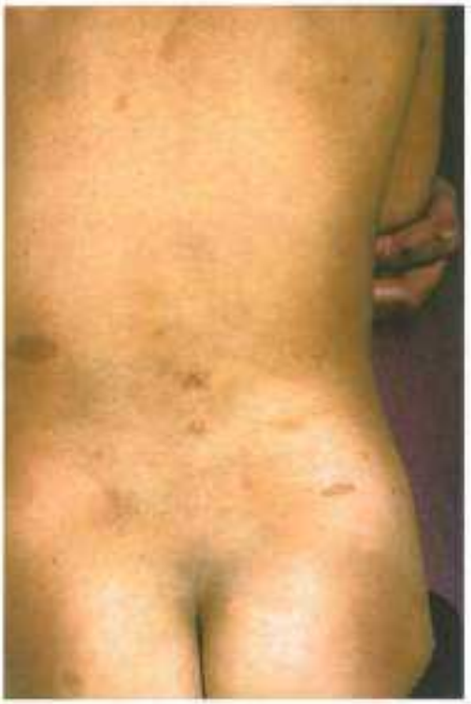


Fig. 20.101 Neurofibromatosis. Several café-au-lait patches are present, which usualy develop in childhood. They may fade with age.

Clinical Features

Symptoms

Pigmented patches (Fig. 20.101) develop during childhood (sometimes they are present at birth), followed by neurofibromas.

Morphology and distribution

There are fawn-coloured, flat patches, usually several centimetres across, which may fade with age. Since they are common in otherwise normal people, six or more café-au-lait patches are deemed necessary for the diagnosis. Small, pigmented macules, similar in appearance to freckles but unlike them in distribution, occur under the axillae (see Fig. 20.95) and in the perineum (Crowe's sign). These are thought to be pathognomonic, although Lisch nodules, which are dome-shaped, translucent papules up to 2 mm in size, in the iris are probably more specific.

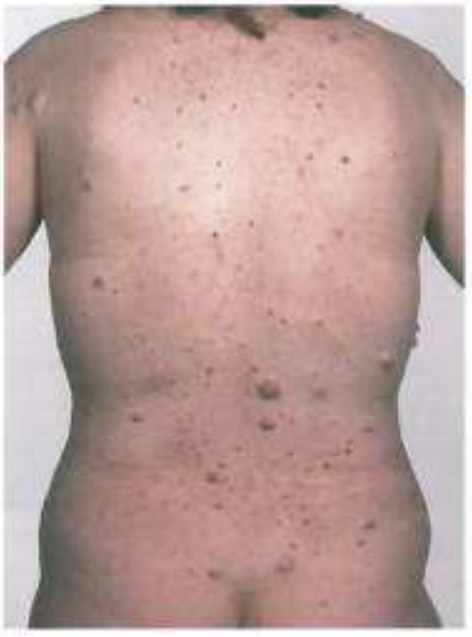


Fig. 20.102 Neurofibromatosis. There are numerous neurofibromas (soft tumours that are easily indented) on the trunk. The café-au-lait patches and axillary freckling confirm the diagnosis.

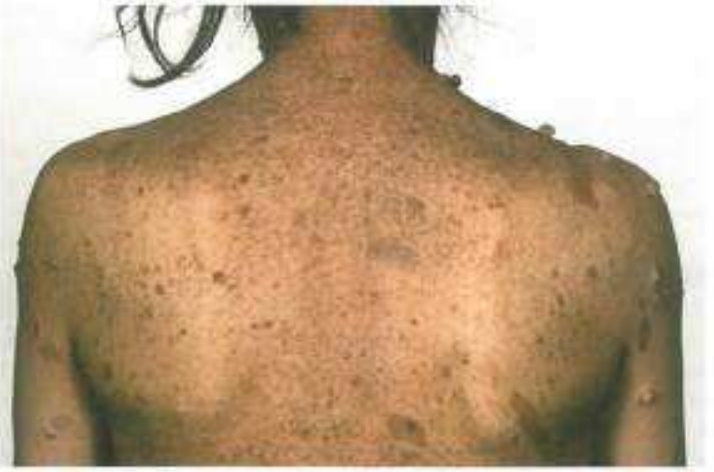


Fig. 20.103 Neurofibromatosis. Multiple café-au-lait patches and neurofibromas are present in this Indian woman and the diagnosis is not difficult.

Neurofibromas (Figs 20.102 and 20.103), derived from peripheral nerves and their supporting structures, develop during childhood and adolescence. There are four types. They may be dermal and consist of soft, sessile, dome-shaped, button-like, pedunculated nodules usually less than 3 cm in diameter, known as *molluscа fibrosa*. Subcutaneous neurofibromas are dermal and adjacent to subcutaneous nerves and may be painful or tender and consist of firm, discrete nodules. Nodular plexiform neurofibromas consist of large networks in the subcutis with direct involvement of the dorsal nerve roots. Diffuse plexiform neurofibromas involve all layers of the skin and may penetrate muscle, bone and viscera. A characteristic physical sign of neurofibromas is that the lesions may be indented on pressure. Sometimes they form large, grotesquely disfiguring, pendulous masses. They may occur anywhere on the body including the oral cavity, but in type 5 they occur in a segmental distribution (Fig. 20.104).

Systemic features

Intracranial neurofibromas may develop in the optic, trigeminal or acoustic nerves, or the lesions may behave as space-occupying growths elsewhere in the brain. The spinal cord and peripheral nerves may be involved. Sarcomatous change may occur in any neurofibroma.

Many other associated disorders are described, particularly endocrine and bony defects. The latter include pseudoarthrosis of the tibia, dystrophic upper thoracic or lower cervical scoliosis, occurring quite rapidly in childhood, and non-progressive sphenoid wing dysplasia. Breast cancer below the age of 50, gastrointestinal stromal tumours of the small bowel and nailbed glomus tumours are more common in *NF-1*.

Management

The diagnosis is straightforward once neurofibromas have developed. In infancy, the café-au-lait macules need to be distinguished from those of Albright's syndrome. The axillary and perineal freckling is helpful and the Lisch nodules are thought to be specific in type 1 neurofibromatosis. Other criteria include optic gliomas and bone deformities such as the absent temporal wing of the sphenoid. Magnetic resonance imaging may aid the diagnosis of optic gliomas, astrocytomas and plexiform neuromas and in type 2 acoustic neuromas. There is no specific treatment except surgical intervention for tumours. Ketotifen is said to be helpful for the pruritus that is sometimes associated with neurofibromatosis.

Tuberous sclerosis

A dominantly inherited neurocutaneous syndrome, characterized by a triad of seizures, mental retardation and skin manifestations.

Aetiology

It has been given the eponym of *epiloia* – epilepsy, low intelligence and adenoma sebaceum – but formes frustes are common. Half have normal intelligence, a quarter do not have fits and the cutaneous changes may be the only presenting symptom. Hamartomas are described in nearly all organs except skeletal muscle. It is quite common. Both sexes are equally affected and 60% are a result of new mutations. Linkage studies show that two genes are involved. One on 9q34 (*TSC1*) encodes the protein hamartin and the other on 16p13 (*TSC2*) encodes tuberin. Both probably function as tumour suppressor genes of the mTOR pathway, which if they are abnormal permit the proliferation of hamartomas. The evidence suggests loss of heterozygosity, that is there is a deletion in one copy of the gene by inheritance or mutation but lesions only develop when there is a somatic mutation in the other allele. This is known as the 'two hit' mechanism of Knudson and is thought to explain the pathogenesis of other disorders such as retinoblastoma, neurofibromatosis and von Hippel–Lindau disease.

Clinical Features

Symptoms

A child may present in infancy because of epilepsy or later on because of a facial rash.

Morphology

There are five skin stigmas:

- **An ovoid ash-leaf patch of hypopigmentation** This patch (Fig. 20.105) is the first cutaneous change to appear during infancy. It may be more easily appreciated by examination under Wood's light. There may be one or several, either on the trunk or limbs. Although they may be white, they are different from vitiligo in that melanocytes are present in normal numbers but contain few melanosomes. In vitiligo, no melanocytes can be found.

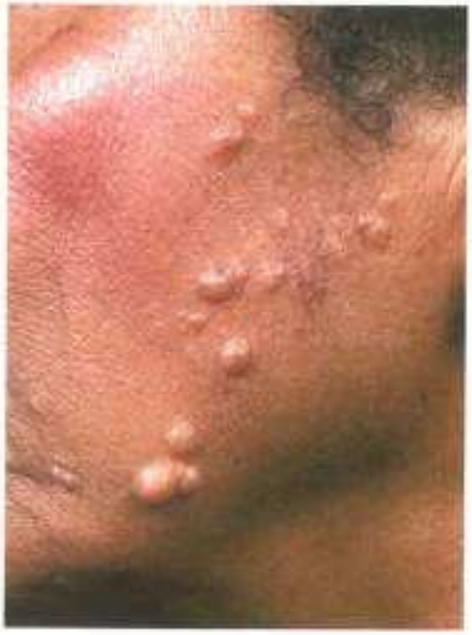


Fig. 20.104 Segmental neurofibromatosis. Type 5 is segmental. There is usually no family history. It is caused by a somatic mutation of the gene *NF-1*. Genetic transmission may occur, but the risk is low as is that of complications.

Fig. 20.105 Tuberous sclerosis. An ovoid, hypopigmented patch is characteristic (ash-leaf patch). Examination under a Wood's light may make it more obvious. (Courtesy of the Institute of Dermatology.)

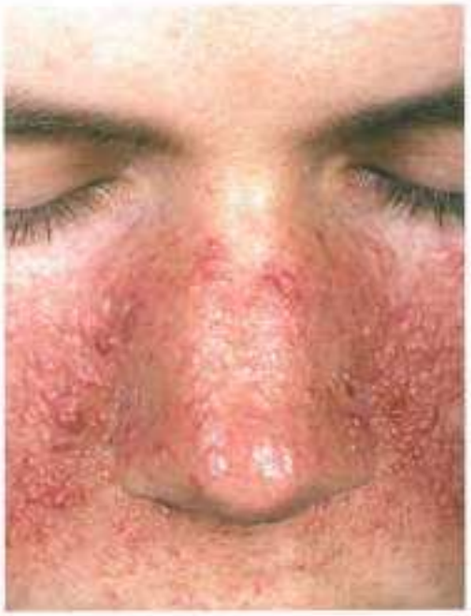


Fig. 20.106 Tuberous sclerosis. Firm flesh-coloured or red papules (adenoma sebaceum) occur on the cheeks, around the nose and on the chin, in childhood.

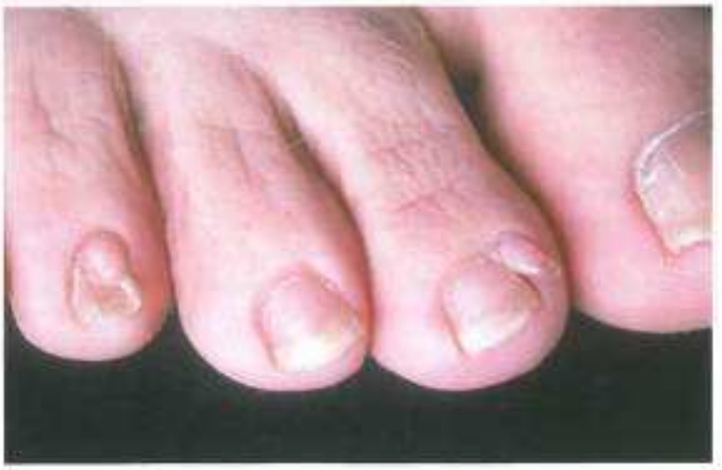


Fig. 20.107 Tuberous sclerosis. Periungual fibromas occur after puberty. They are characteristic and known as Koenen tumours.

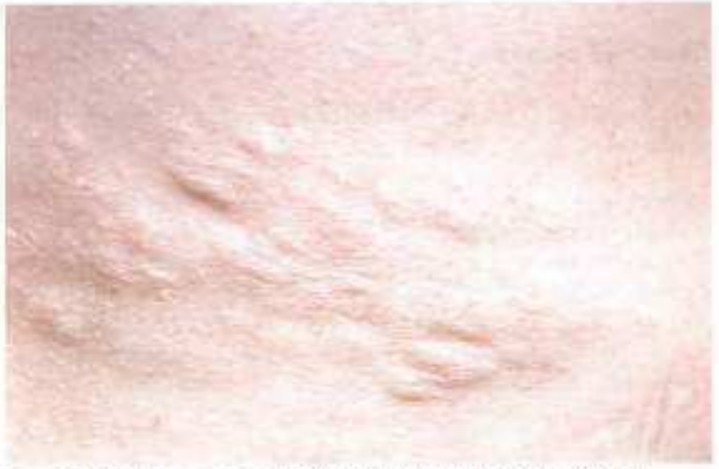


Fig. 20.108 Tuberous sclerosis. Slightly raised papules with a soft 'peau d'orange' surface represent a connective tissue naevus and are called shagreen patches. (Courtesy of Dr A. C. Pembroke.)

- **Adenomata sebaceum** These are in reality angiofibromas and appear in childhood, from 5 years onwards. They occur on the face, particularly around the sides of the nose, but may also occur on the chin, cheeks (Fig. 20.106) and forehead (very characteristic and may even be present at birth). They consist of small red or yellow tumours, about 2 mm in diameter, that occur symmetrically.
- **Periungual fibromas** These fibromas (Fig. 20.107) appear later after puberty, and may be the only manifestation.
- **Shagreen patches** These are connective tissue naevi on the trunk, usually the lumbosacral region. They are skin coloured but slightly raised, with a soft surface (Fig. 20.108) simulating that of orange peel.
- **Fibromatous nodules** These occur on the forehead or scalp.

Systemic features

Fibrous nodules are also found on the gums, palate, tongue and in the larynx. There are large pits on the labial surfaces of the dental enamel. There may be tumours of the heart, kidney, liver, thyroid, gastrointestinal tract, brain and eye. Retinal phacomata are diagnostic. They consist of grey or yellow plaques near the optic disc. They may also occur in neurofibromatosis. Astrocytomas, if they occur, tend to present in childhood. Renal changes consist of cysts; angiomyolipomas and cardiac rhabdomyomas may be diagnosed prenatally.

Management

The diagnosis is usually quite straightforward when the typical ash-leaf patches are found. Computed axial tomography aids diagnosis, as intraventricular calcified nodules may be found even in infants. Magnetic resonance imaging may show subependymal nodules and cortical and white matter tubules. There is no specific treatment, but genetic counselling is essential. In vitro fertilization with donor eggs has been advocated for affected females. For the adenoma sebaceum, cautery and laser treatment have been tried.

Ectodermal dysplasia

Ectodermal dysplasia is a clinically and genetically heterogeneous group, comprising over 170 rare disorders resulting from abnormal embryonic development of the ectoderm. There is absent, incomplete or delayed development of one or more of the four epidermal appendages of hair, teeth, nails and sweat glands, in decreasing order of frequency of involvement. The oral mucosa may also be affected. Classification is confusing. One system assigns the syndrome numerically depending on how many appendages are involved. 1 is hair, 2 dental, 3 nail and 4 sweat gland dysplasia. Hypohidrotic X-linked ectodermal dysplasia would be an example of subgroup 1-2-3-4 and the trichorhinophalangeal syndrome would be an example of subgroup 1-2-3 because sweating is normal. Abnormal genes include *EDA1* (ectodysplasin-A1), *EDA3*, *EDAR* (*EDA-A1* receptor) and *EDAR ADD* (*EDAR*-associated death domain) and immunodeficiency. *EDA1* is a member of the tumour necrosis factor ligand superfamily, which is expressed in normal teeth, skin and hair. Three syndromes are described here, hypohidrotic ectodermal dysplasia, trichorhinophalangeal syndrome and the ectrodactyly, ectodermal dysplasia, cleft lip/palate (EEC) syndrome.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

A syndrome characterized by partial or complete absence of sweat glands, sparse hair, hypo- or anodontia and nail changes.

Aetiology

It is usually inherited as an autosomal recessive so the majority of those affected are male, although female carriers may show some changes. Linkage studies have mapped the disorder to Xq12,13.1, producing a mutant form of a transmembrane protein that is thought to have a role in epithelial–mesenchymal signalling. There is also an autosomal dominant type that is indistinguishable except that it occurs in both sexes and the sweat glands are less affected. Sweating is normal in *hidrotic ectodermal dysplasia* (*Clouston syndrome*). There is a characteristic nail dystrophy (nails which are thickened, striated, may be discoloured and grow slowly). Diffuse hyperkeratosis of the palms and soles occurs with alopecia, which is usually manifested by adolescence. The histology of hypohidrotic ectodermal dysplasia shows that the eccrine sweat glands are absent or rudimentary and that there is often a reduction in the number of hair follicles and sebaceous glands.

Clinical Features

Symptoms

The child may present with heat intolerance, dental abnormalities or sparse hair.

Morphology and distribution

- **Scalp and body hair** Hair is sparse, dry, fine and short (Fig. 20.109) or absent (Fig. 20.110). The eyebrows may be absent.
- **Skin** The skin may be smooth, dry and finely wrinkled, especially around the eyes, and may age prematurely.
- **Teeth and mouth** The teeth may be absent or the primary teeth conical (Fig. 20.111) and the secondary curved. There may be gum disorders and a dry mouth.
- **Sweating** The reduction or absence of sweating is associated with poor heat tolerance and discomfort. Hyperpyrexia may result and cause fever to a level that sometimes constitutes a medical emergency, especially in infants, causing brain damage.
- **Facies** There may be prominent frontal ridges and chin, saddle nose and sunken cheeks. The lips are thick and everted (Fig. 20.112). Growth may be stunted and sometimes there is mental retardation.

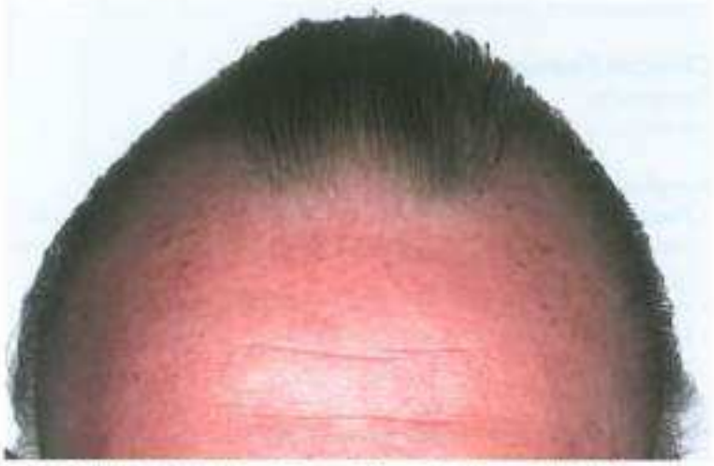


Fig. 20.109 Hypohydrotic ectodermal dysplasia. The scalp hair is fine, sparse and dry. The eyebrows may be absent.

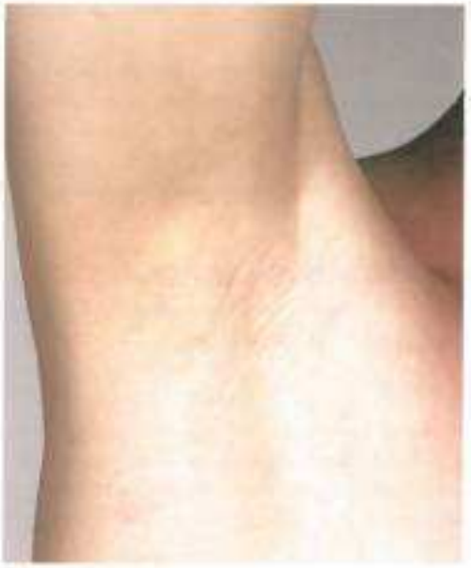


Fig. 20.110 Hypohidrotic ectodermal dysplasia. The axillary hair is absent and scalp hair is fine and sparse. Sweating is reduced or absent, resulting in poor heat tolerance and hyperpyrexia.

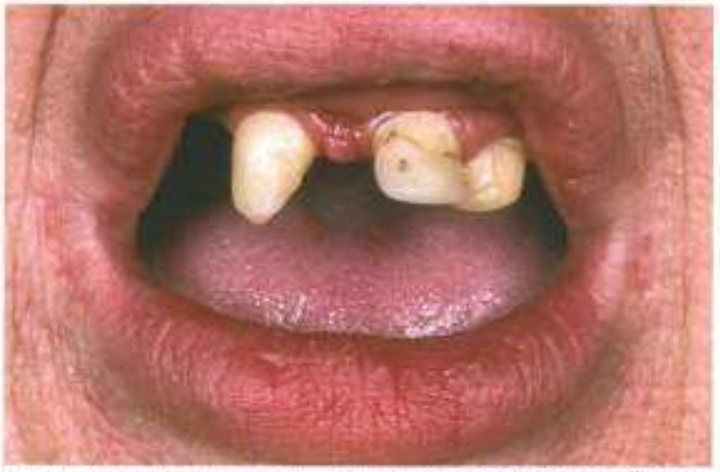


Fig. 20.111 Hypohidrotic ectodermal dysplasia. The dental abnormalities are diagnostic. There may be absent or supernumerary teeth. The incisors may be peg shaped.

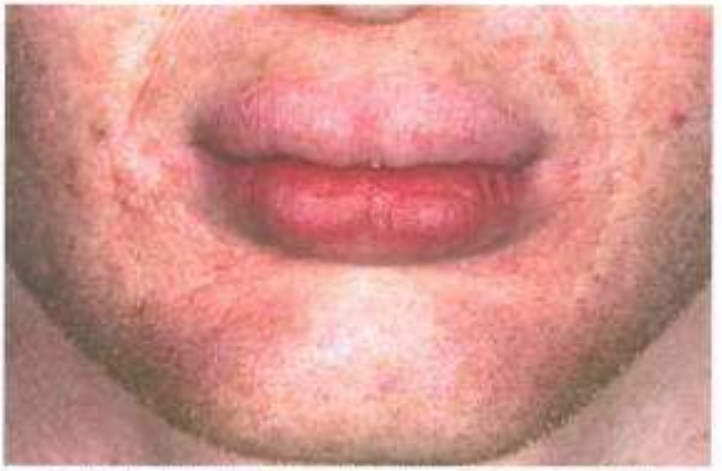


Fig. 20.112 Hypohidrotic ectodermal dysplasia. There is a characteristic facies of thick, everted lips, prominent frontal ridges and chin, sunken cheeks and saddle nose.

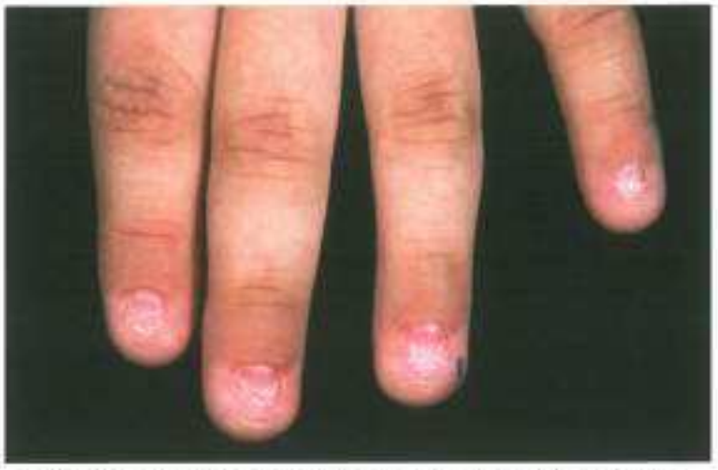


Fig. 20.113 Hypohidrotic ectodermal dysplasia. The nails may be thin and brittle and break away easily.

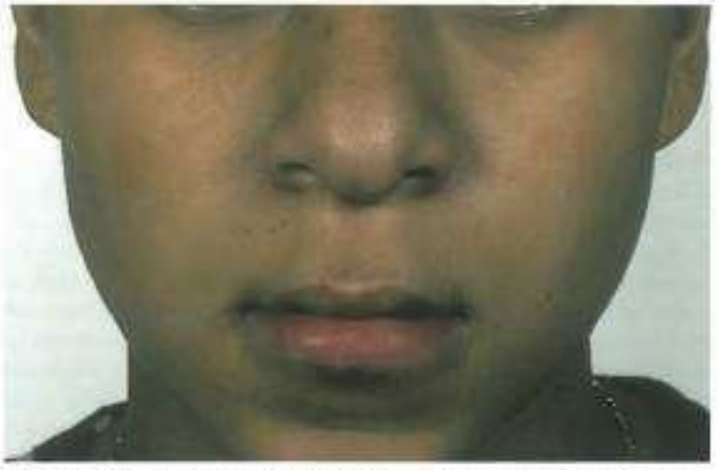


Fig. 20.114 Trichorhinophalangeal syndrome. There is a large, pear-shaped nose above a high philtrum. A projection of normal skin below the lower lip is characteristic.

- **Nails** In half of the patients, these are brittle, thin or ridged (Fig. 20.113).
- **Atopic disorders** These are often present.

Management

Although the diagnosis can be confirmed by skin biopsy, the dental abnormalities are usually characteristic enough. Starch iodide tests of sweat gland function are also helpful. There is no specific treatment for the disorder, but expert dental care is required and physical exertion and hot environments should be avoided. Prenatal diagnosis is possible.

TRICHORHINOPHALANGEAL SYNDROME

A rare inherited disorder with characteristic pear-shaped nose, abnormal swelling of the phalanges, sparse hair and reduced growth.

Aetiology

The cause is unknown. Trichorhinophalangeal syndrome appears to be determined by an autosomal dominant gene of variable expressivity. Women are affected more than men. There are two types described. Type 1 is caused by a small deleted segment of 8q24.12 and type 2 by a slightly larger deletion extending from 18q 24.11 to 18q 24.13. Type 2 is sometimes known as the *Langer–Giedion syndrome*. Multiple exostoses, microcephaly, loose and redundant skin and multiple acquired naevi distinguish it from the type 1 syndrome.

Clinical Features

Symptoms

The child may present because of abnormal hair growth.

Morphology and distribution

- **Facies** The facies is distinctive, with a large, pear-shaped nose above a high philtrum (Fig. 20.114). A projection of normal skin below the lower lip is characteristic.
- **Hair** The scalp hair is fine, brittle and sparse (Fig. 20.115).
- **Hands** The proximal interphalangeal joints may be swollen and the fingers angulated (Fig. 20.116).
- **Nails** The nails may be thin and brittle.
- **Stature** Those affected are short.

Management

The diagnosis is a clinical one. There is no known treatment.

Fig. 20.115 Trichorhinophalangeal syndrome. The hair is fine, brittle and sparse. (Courtesy of Dr Michèle Clement.)

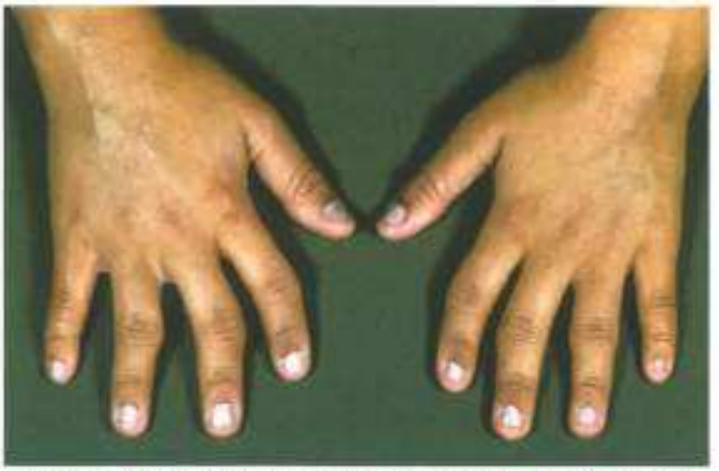


Fig. 20.116 Trichorhinophalangeal syndrome. The proximal phalangeal joints may be swollen and the fingers angulated. The nails may be thin and brittle. (Courtesy of Dr Michèle Clement.)

ECTRODACTYLY, ECTODERMAL DYSPLASIA CLEFT LIP/PALATE (EEC) SYNDROME

A highly variable autosomal dominant disorder of ectodermal dysplasia with a characteristic lobster claw deformity of the hand, cleft lip and palate, abnormal teeth and hair.

Aetiology

In some but not all there is deletion in the chromosome region 17q11.2–q21.3. Some have a cleft palate and the lobster claw deformity but others do not. All have ectodermal dysplasia and the condition is thought to be a contiguous gene syndrome with probably the ectodermal gene in the middle. There are mutations in *TP63*, a member of the tumour *TP53* gene family which acts as a key transcription factor in limb, epithelial and craniofacial development, resulting in various autosomal dominant syndromes, including EEC, split-hand/foot malformations, *Hay–Wells syndrome* (ankyloblepharon, ectodermal dysplasia and clefting), *Rapp–Hodgkin syndrome* (similar to AEC, but without the partial eyelid fusion and a characteristic facies of microstomia and midline hypoplasia), *ADULT* (acro-dermato-ungual-lacrimal-tooth) syndrome. There is freckling, mammary gland hypoplasia, but no clefting. EEC is the prototype of *TP63* mutations and is the most prevalent.

Clinical Features

Symptoms

The infant may present with a cleft lip, palate and abnormal hand.

Morphology and distribution

- **Skin** may be dry and eczematous
- **Nails** may be dystrophic
- **Eyelashes and eyebrows** may be sparse
- **Sweating** may be reduced or increased
- **Hair** The hair may be sparse, wiry and hypopigmented.

Systemic features

- **Mouth** There may be a cleft lip and palate and often lacrimal duct stenosis.
- **Teeth** These may be peg shaped with defective enamel.
- **Larynx** The normal mucosae of the laryngeal folds may be absent and the voice may be slightly abnormal (as it may in anhidrotic ectodermal dysplasia).
- **Hearing** There may be conductive or sensorineural deafness.
- **Hands** A striking abnormality is the lobster claw deformity (Fig. 20.117).
- **Breasts** Mammary gland and nipple hypoplasia.

Management

Genetic counselling may be helpful.

HEREDITARY HAEMORRHAGIC TELANGIECTASIA

An autosomal dominant condition of blood vessels, distinguished by mucocutaneous telangiectasia and resulting in widespread haemorrhage.

Aetiology

Also known as the *Rendu–Osler–Weber* syndrome, it is due to loss of function mutations in the *ENG* (endoglin) gene in HHT 1 on 9q33-34 and in *ACVRL1* in HHT 2 on chromosome 12q13, which compromise vessel wall integrity. Expression and onset are variable. Patients may not be aware of a family history and about 10% do not bleed. In homozygous individuals, the disorder is liable to be fatal. Blood vessels throughout the body may be affected. They are dilated and thin walled; there may be arteriovenous malformations and aneurysms.

Clinical Features

Symptoms

The condition usually presents before puberty, particularly with epistaxis, gastrointestinal, pulmonary or genitourinary haemorrhage. The cutaneous lesions often do not appear until adult life.

Morphology

Widespread, tiny telangiectases occur.

Distribution

Oral lesions are almost always present, especially on the tip and dorsum of the tongue (Fig. 20.118) and on the palate. Lesions are found on the

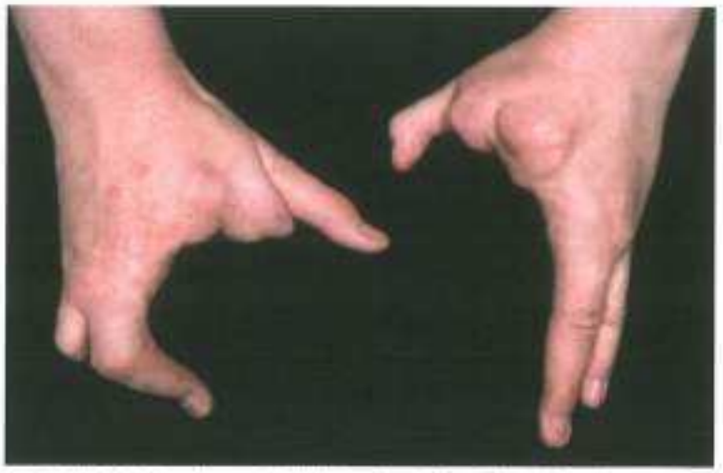


Fig. 20.117 EEC syndrome. The lobster claw deformity is a striking abnormality. Cleft lip and palate and abnormal hair, teeth and laryngeal mucosa may be present.

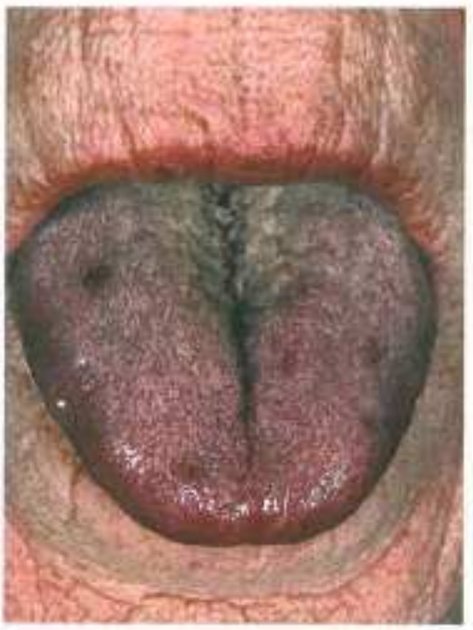


Fig. 20.118 Hereditary haemorrhagic telangiectasia. Tiny, red, telangiectatic lesions occur on the tongue, lips and around the mouth. Recurrent haemorrhage is common, especially from the nose and gut.

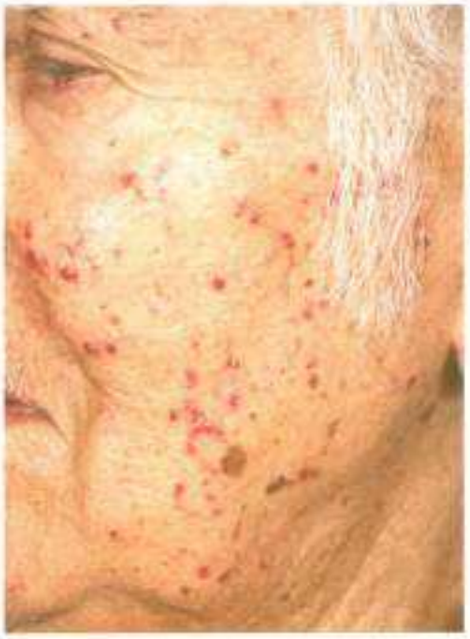


Fig 20.119 Hereditary haemorrhagic telangiectasia. Punctate telangiectasia on the face are characteristic. There are mutations in the genes, which encode a glycoprotein expressed mainly on vascular endothelial cells.

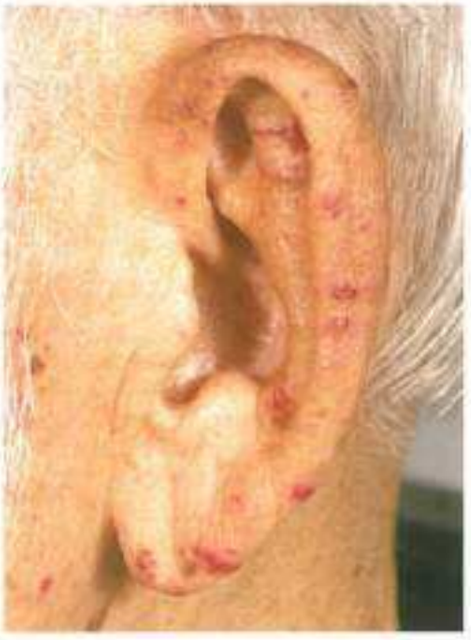


Fig 20.120 Hereditary haemorrhagic telangiectasia. Lesions on the ears are characteristic. It is an autosomal dominant condition associated with systemic haemorrhage.

nasal septum and the nasopharynx. The face (Fig. 20.119), lips, ears (Fig. 20.120), hands, around the nails, chest and feet can be affected.

Management

There is no specific treatment, except for supportive measures when bleeding occurs and embolization, laser therapy and surgical resection of arteriovenous malformations. The cutaneous, oral and nasal physical signs should point to the diagnosis in a patient bleeding from the gastrointestinal or nasal mucosa.

Proteus syndrome

A rare asymmetrical overgrowth of a variety of tissues particularly resulting in skeletal abnormalities (including hemihypertrophy and macrodactyly), cerebroid hyperplasia of the soles and epidermal and vascular naevi.

Aetiology

It occurs sporadically in both sexes and is probably a genetic mosaicism that would be lethal in its pure form. It is a multifocal, asymmetrical developmental disorder of ectoderm and mesoderm resulting in dysmorphism with a polyclonal clinical expression. It is named after Proteus, a character in Greek mythology, known as the old man of the sea, who could change his shape at whim, usually in order to avoid capture. The term stresses the polymorphic nature of the disorder. Widespread dermal hypoplasia or aplasia also occurs in this syndrome in addition to the dermal hyperplasia and this is thought to be an example of twin spotting, whereby one allele accounts for dermal overgrowth and the corresponding allele is responsible for a diminished growth of dermal fibroblasts. The two alleles balance, producing normal dermal tissue, but if at an early stage of embryogenesis, somatic recombination results in two daughter cells homozygous for either allele, there would be one stem cell for circumscribed dermal overgrowth and the other for dermal hypoplasia.

Clinical Features

Symptoms

Usually an overgrowth of part of the body is present at birth.

Morphology and distribution

- **Naevi** Linear or whorled epidermal naevi (Fig. 20.121).
- **Capillary, venous, lymphatic and combined slow flow malformations identical to Kippel–Trenaunay syndrome** Deep vein thrombosis and pulmonary embolism are common.
- **Lipoma-like subcutaneous hamartomas.**
- **Cerebriform hyperplasia** On the soles and sometimes the palms (being either connective tissue naevi or lipomas histologically).

Systemic features

- **Tumours** Bilateral ovarian cystadenomas and parotid monomorphic adenomas may present in the second decade. Lung cysts are common.
- **Skeletal abnormalities** Hemihypertrophy of the limbs, and sometimes the scalp, face and trunk; macrocephaly; macrodactyly (Fig. 20.122) and random deviations of the digits; scoliosis; and exostoses.

Management

The differential diagnosis is of other disorders causing hemihypertrophy such as Klippel–Trenaunay–Weber syndrome, neurofibromatosis, Maffucci's syndrome (see Fig. 8.66) and Bannayan syndrome. It is probable that the Elephant Man was suffering from this condition. Treatment is not satisfactory.

Syndromes associated with DNA instability

Normal individuals can repair cellular DNA that has been damaged by radiation or environmental carcinogens. Inherited disorders characterized by photosensitivity and defective DNA repair either have defects in nucleotide excision repair (xeroderma pigmentosum, Cockayne syndrome and the photosensitive form of trichothiodystrophy) or chromosomal instability (Bloom's and Rothmund–Thomson syndromes).

Bloom's syndrome is an autosomal recessive disorder of photosensitivity, café-au-lait macules, areas of hypopigmentation, facial telangiectasia, short stature, hypogonadism and a high frequency of lymphoma, leukaemia and adenocarcinoma of the gastrointestinal tract. It particularly affects Ashkenazi Jews and there are mutations in the *BLM* gene (*RECqL3*) resulting in chromosomal instability. It is characterized by cytogenetic abnormalities in cultured fibroblasts and lymphocytes (increased spontaneous sister chromatid exchanges and chromosome abnormalities,

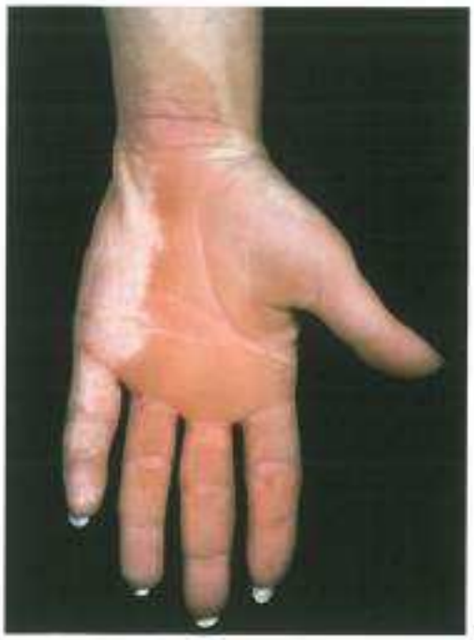


Fig. 20.121 Proteus syndrome. Epidermal naevi, particularly involving the extremities, and other naevi (vascular, lymphatic and connective tissue) are common.

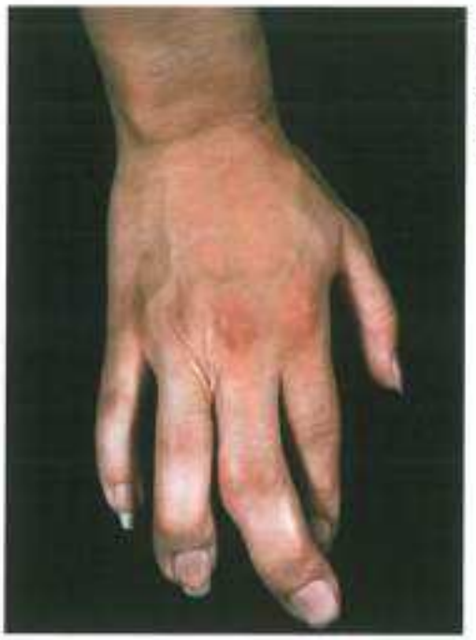


Fig. 20.122 Proteus syndrome. Macrodactyly, deviation of the digits and other skeletal abnormalities may suggest the diagnosis.

including increased chromosome breakages and rearrangements producing quadriradial configurations). The gene encodes DNA helicase and is located on chromosome 15. There is a characteristic facies of a long narrow head, receding chin, hypoplastic cheeks and prominent nose.

Cockayne's syndrome is a rare autosomal disorder of photosensitivity, premature ageing of the skin, mental deficiency, short stature, ocular and neurological abnormalities and a Mickey Mouse appearance. There is a reduced ability to repair actively transcribed genes, which may be critical during cellular development and differentiation and results in the skeletal and nervous system abnormalities.

XERODERMA PIGMENTOSUM

A heterogeneous collection of photosensitive disorders that result in premature ageing and cutaneous neoplasia including melanoma, caused by enzymatic failure to repair solar-damaged epidermal DNA.

Aetiology

Xeroderma pigmentosum is inherited as an autosomal recessive and occurs in both sexes and all races but is more common in Japan. Cleaver demonstrated in 1968 that fibroblasts from these patients lack the normal capacity to repair ultraviolet light-damaged skin. This abnormality is found in all cells, including amniotic cells, so prenatal diagnosis is possible. In the majority, there is failure in enzymatic excision of the thymine dimers that occur when thymidine base pairs in DNA are irradiated. Most of the genes involved in nucleotide excision repair have now been cloned. Xeroderma pigmentosum is a heterogeneous disease and there are at least eight complementation subgroups (A–G) and a xeroderma pigmentosum variant. In the xeroderma pigmentosum variant, there is normal nucleotide excision repair, but defective post-replication repair. The photoageing and photocarcinogenesis is less exaggerated than in xeroderma pigmentosum. These are demonstrated by culturing fibroblasts from two different affected patients so that their nuclei are fused in the same cytoplasm. If those nuclei have the same defect, ultraviolet irradiation will lead to defective repair; if they are different, the one nucleus will supply what the other is lacking and the DNA repair mechanism will be normal. The latter patients are then said to be in different complementation groups. 25% of patients develop severe neurological deterioration (sensorineural hearing loss, ataxia, dysphagia, and decreasing cognition). The mutations in *XPA* cause particularly severe neurodegeneration, often beginning in the second decade.

The *de Sanctis–Cacchione syndrome* is xeroderma pigmentosum with other abnormalities such as microcephaly, severe mental deficiency, dwarfism, hypogonadism, deafness, choreoathetosis and ataxia. There is another variant, known as the *pigmented xerodermoid*, which involves the delayed onset of xeroderma pigmentosum until the third or fourth decade. Mutations in the *XPD* gene lead to three distinct phenotypes, xeroderma pigmentosum, xeroderma pigmentosum and Cockayne's syndrome, and trichothiodystrophy. This clinical heterogeneity is probably because the *XPD* gene has a dual role, one for DNA repair and the other forms one of the nine constituent subunits of the basal transcription factor TFIIH, which leads to trichothiodystrophy.

Clinical Features

Symptoms

The baby is normal at birth but episodes of extreme photosensitivity occur, with acute sunburn, within a few months; this is followed in some patients by persistent erythema (Fig. 20.123).

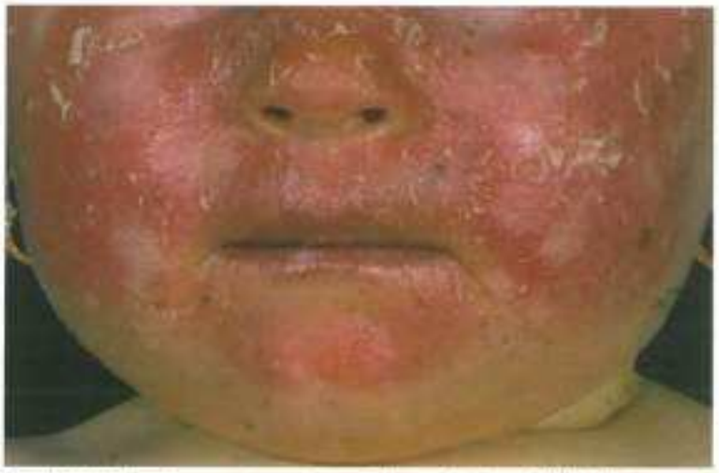


Fig. 20.123 Xeroderma pigmentosum. Extreme photosensitivity is the key feature of this condition. Persistent erythema occurs after seemingly innocent solar exposure. Lentigines are already apparent.

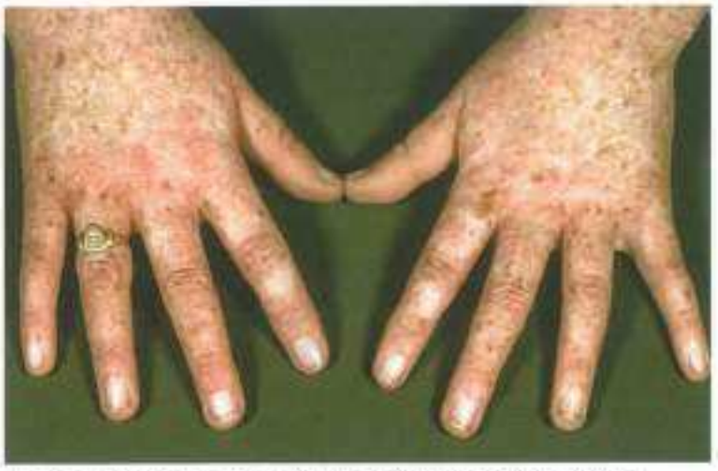


Fig. 20.124 Xeroderma pigmentosum. Dryness (xeroderma), lentigines (pigmentosum), angiomas and telangiectasia occur in exposed skin early in childhood. There is a failure to repair DNA damaged by irradiation.

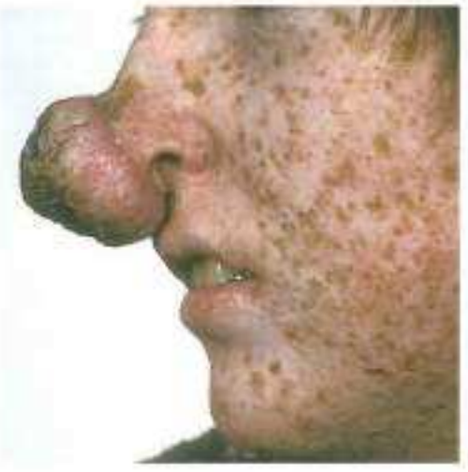


Fig. 20.125 Xeroderma pigmentosum. Malignant change occurs early in life. This keratoacanthoma developed in a 12-year-old girl. The lesion did, however, resolve spontaneously.

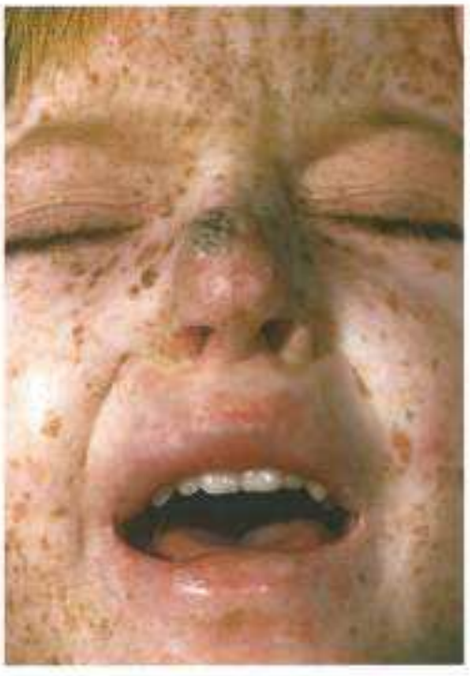


Fig. 20.126 Xeroderma pigmentosum. Photosensitivity occurs in infancy. Solar lentigines and skin cancer (in this case a squamous cell carcinoma on the nose) develop in childhood.

Morphology and distribution

Masses of freckles (pigmentosum) develop in exposed areas (Fig. 20.124), associated with dryness (xeroderma), angiomas and telangiectasia. There is a variety of premalignant and malignant lesions, including solar keratoses, basal cell carcinomas, keratoacanthomas (Fig. 20.125), squamous cell carcinomas (Fig. 20.126) and malignant melanomas.

Systemic features

The eyes are almost always involved, with photophobia, conjunctivitis, ectropion, symblepharon and ulceration. Pigmented macules of the conjunctivae are common. Patients are usually small in stature and have poor physical development. Some are mentally retarded.

Death before the end of adolescence was formerly considered the norm, either from metastasis from one of the skin tumours or infection, to which patients are often abnormally susceptible. However, there is considerable variation in the manifestations of the disease.

Management

The diagnosis is not difficult once the freckling begins to occur. It may be confirmed by sophisticated studies of DNA repair in fibroblasts that have been exposed to ultraviolet irradiation. Antenatal diagnosis by amniocentesis is possible for families where the existence of the disorder is known. It is imperative for the child to be protected from sunlight by staying indoors during the middle of the day, by wearing photoprotective clothing and through the obsessional use of sunscreens. The skin must be closely supervised with a view to the early diagnosis and treatment of malignant tumours. Ophthalmological supervision is also necessary. Retinoids are reported as being of benefit in slowing the onset of tumours. Screening of relatives should be undertaken.

DYSKERATOSIS CONGENITA

A rare inherited condition of atrophy and pigmentation of the skin, nail dystrophy, leucoplakia, ocular, gastrointestinal, pulmonary and haematological abnormalities; and an increased risk of carcinoma.

Aetiology

There are mutations in the *hTERT* and *hTR* genes, which encode telomerase reverse transcriptase and telomerase RNA respectively. Telomeres shorten with each cell division and telomerase is necessary for telomere maintenance in tissues of high turnover, such as the bone marrow, bronchoalveolar epithelium and skin. Short telomeres activate a DNA damage response leading to cell death or cell cycle arrest. Pulmonary fibrosis is present in 20%. Bone marrow failure (aplastic anaemia or myelodysplastic syndrome) is the commonest form of death. The condition is usually inherited as an X-linked recessive, but occasionally as an autosomal dominant, which can present in adult life and often lacks skin manifestations.

Clinical Features

Symptoms

The child is normal at birth. Pigmentary abnormalities begin before 5 years of age.

Morphology and distribution

There is fine, reticulate, brown discoloration around the neck (Fig. 20.127) and thighs, often with atrophy and telangiectasia, which simulates poikiloderma. The exposed parts of the face and backs of the hands are red and atrophic with macular pigmentation, but it may become extensive (Figs 20.128 and 20.129). The skin becomes transparent, wrinkled

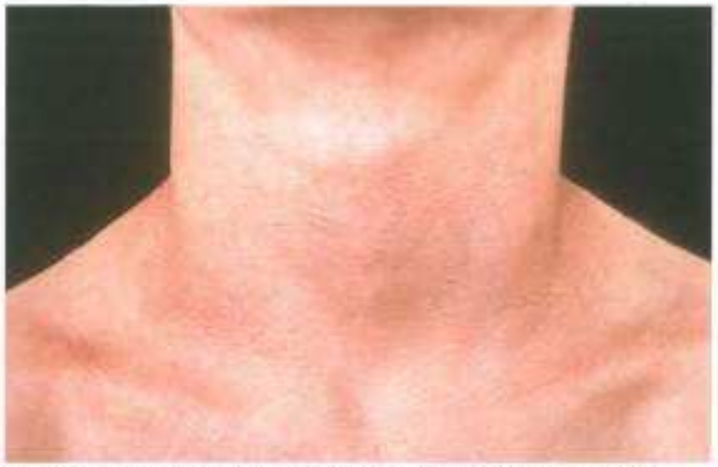


Fig. 20.127 Dyskeratosis congenita. A fine, reticulate, brown discoloration occurs around the neck, often with atrophy and telangiectasia simulating poikiloderma. (Courtesy of Dr David Atherton.)

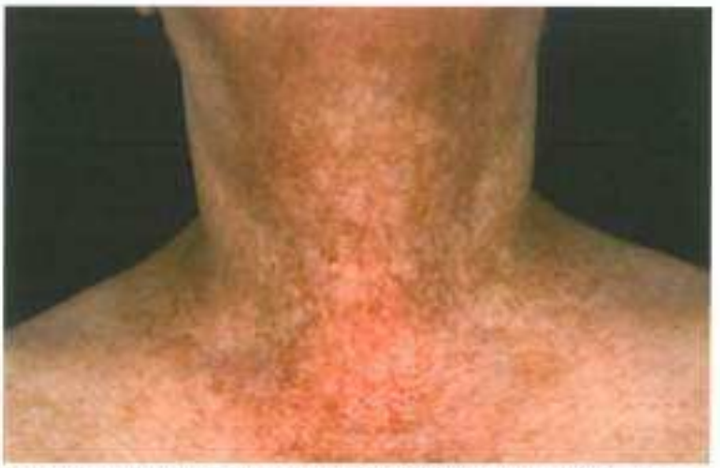


Fig. 20.128 Dyskeratosis congenita. He had a prominent mottled reticular pigmentation around the neck, torso and arms for as long as he could remember, which was not diagnosed until he was in his sixties.

and atrophic. The palms and soles are hyperkeratotic and there is hyperhidrosis.

The nail dystrophy (Fig. 20.130) is apparent within the first or second decade. The nails are usually shed, to leave either horny plugs or total destruction. Suppurative paronychia is common. Leucoplakia may occur anywhere, but particularly in the mouth (Fig. 20.131) and carcinoma is a common sequela.

Management

The diagnosis is made using the FISH technique for shortened telomere length. It may be confused with Rothmund–Thomson syndrome, but there are no nail changes or leucoplakia or Fanconi's anaemia, where there are also pancytopenia and pigmentary anomalies (generalized hyperpigmentation, especially in the flexures, guttate hypopigmentation and CALMS), but there are skeletal malformations (especially aplasia radii) and chromosomal fragility (unlike dyskeratosis congenita). The disorder is usually fatal because of the high incidence of carcinoma of the digestive tract, buccal cavity or pharynx, or bone marrow failure in the second or third decade. It may be treated with bone marrow transplantation.

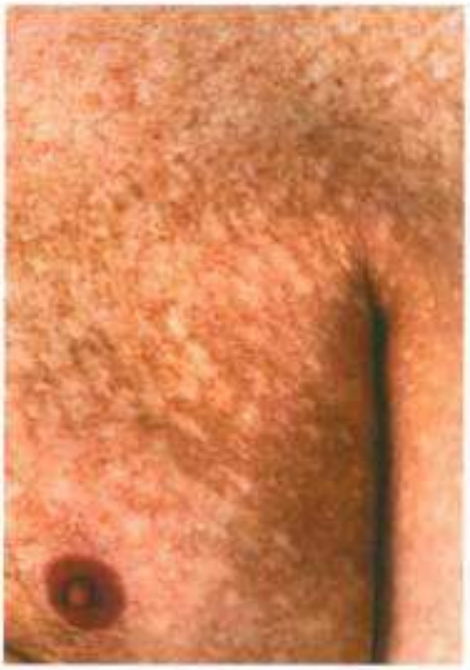


Fig. 20.129 Dyskeratosis congenita. He ultimately developed pulmonary fibrosis, which was labelled idiopathic until he developed bone marrow failure and referred to the haemato-oncologists at our institution, who requested a dermatology opinion on the reticulate pigmentation which he had had for 60 years.

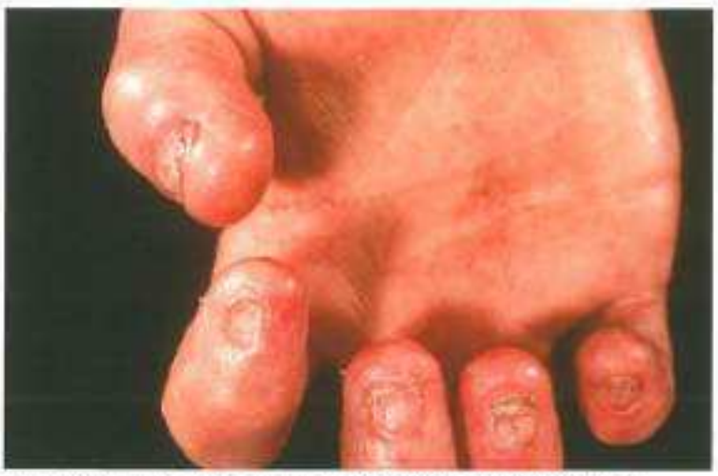


Fig. 20.130 Dyskeratosis congenita. The nails are shed and destroyed. (Courtesy of Dr David Atherton.)

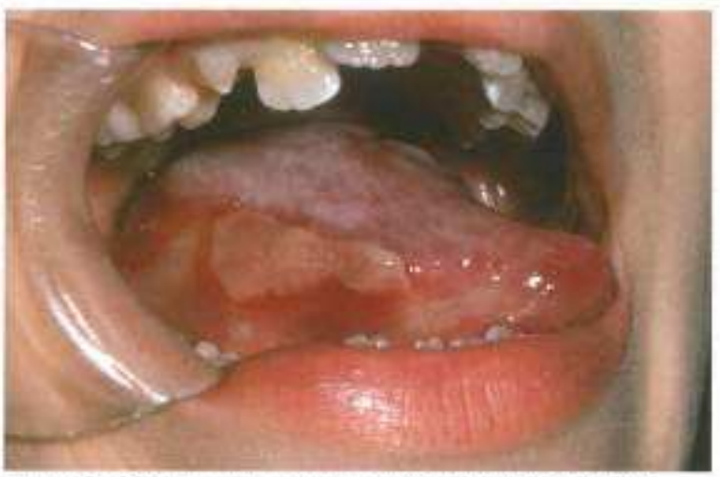


Fig. 20.131 Dyskeratosis congenita. Erosions of the tongue are followed by white patches (so called leucoplakia) of epidermal dysplasia. (Courtesy of Dr David Atherton.)

ATAXIA TELANGIECTASIA

An autosomal recessive disorder associated with progressive cerebellar ataxia, ocular and cutaneous telangiectasia, immunodeficiency and increased sensitivity to ionizing radiation (Louis–Bar disease).

Aetiology

It is inherited as an autosomal recessive and caused by mutations in *ATM* which encodes a phosphatidyl inositol 3-kinase-like serine/threonine protein, which activates apoptosis and cell cycle repair responses to DNA damage. Its frequency is approximately 1 homozygote per 40 000 births and, therefore, heterozygotes are relatively common. There are abnormalities in both the humoral (in particular decreased IgA, IgE and IgG2) and the cell-mediated immune system, with an increased susceptibility to infection, leukaemia and lymphoma. The gene is located on 11q22-23.

An IgM macroglobulin may be present. All patients have a raised α-fetoprotein and carcinoembryonic antigen, which are, therefore, diagnostic markers. There is a high frequency of spontaneous chromosomal abnormalities in the leucocytes of these patients. X-irradiation of cultured cells from a subject with ataxia telangiectasia results in a high proportion of chromosomal breakages. There is an increased risk of breast cancer in female carriers.

Clinical Features

Symptoms

The condition usually starts in early childhood, with ataxia.

Morphology

Telangiectasia is the striking physical sign. There is also an increased incidence of vitiligo and café-au-lait patches.

Distribution

The conjunctiva (Fig. 20.132) and skin of the cheeks, eyelids, neck, pinna, backs of the hands and the antecubital and popliteal fossae.

Systemic features

There is progressive neurological deterioration, defective spermatogenesis, premature ageing, growth retardation, insulin-resistant diabetes mellitus and infections of the lungs and sinuses. Approximately 10% develop lymphomas and lymphoblastic leukaemias before 15 years of age.

Management

The clinical picture is distinct. Cutaneous signs have usually developed by 3 years of age and the neurological signs by 6 years. By puberty, the patient is unable to walk, has slurred speech and experiences difficulty with eye movements. Gradual mental deterioration occurs. The diagnosis can be made prenatally.

ROTHMUND–THOMSON SYNDROME

A photosensitivity that results in poikiloderma and skin cancer, short stature, endocrinopathy, small hands, hypogonadism, sparse hair and juvenile cataracts.

Aetiology

It is usually inherited as an autosomal recessive, and reduced unscheduled DNA synthesis caused by ultraviolet C irradiation has been reported.

There are mutations in *RECqL4*, which encodes a DNA helicase and is responsible for unwinding double-stranded DNA into single-stranded DNA. Other premature ageing and malignancy-associated syndromes have similar mutations: *RECq2/BLM* in Bloom's and *RECq3/WRN* in Werner's syndrome.

Clinical Features

Symptoms

The skin is normal at birth but photosensitivity is quickly apparent.

Morphology

There are transitory plaques of erythema and oedema, particularly and a tendency to blistering of the skin, which diminishes as the patient grows older. Gradually, atrophy and telangiectasia are followed by mottled pigmentation and poikiloderma, which resemble chronic radiodermatitis (Fig. 20.133).

Distribution

The face is affected, in particular the cheeks, followed by the forehead, chin and ears. The backs of the hands, forearms and lower legs are also affected and subsequently less-exposed areas such as the trunk and buttocks.

By adolescence, keratoses, and subsequently squamous cell carcinomas, develop, particularly on the backs of the hands and lower legs.

The scalp hair is sparse and fine, even absent. The eyelashes, eyebrows, pubic and axillary hair are diminished. The nails may be normal or small and dystrophic. The teeth, if not normal, may be small and prone to caries.

Fig. 20.132 Ataxia telangiectasia. Dilated, tortuous blood vessels occur over the eyeball. Similar lesions occur over the ears and cheeks. (Courtesy of the Institute of Dermatology.)

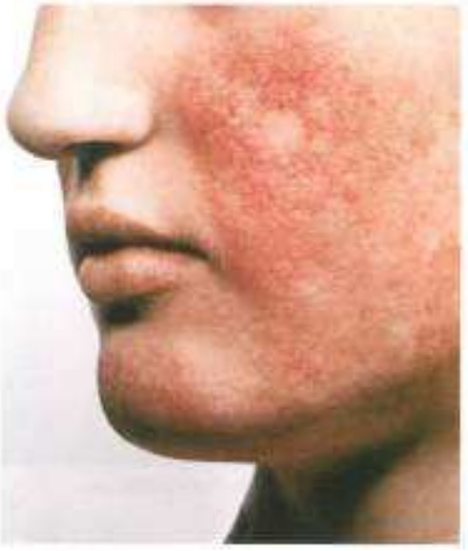


Fig. 20.133 Rothmund–Thomson syndrome. Photosensitivity results in mottled pigmentation, atrophy and telangiectasia (poikiloderma) in youth. Subsequently, cutaneous malignancies develop.

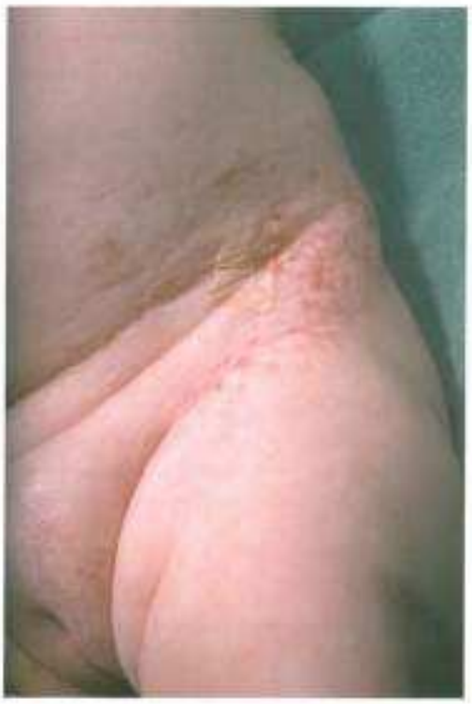


Fig. 20.134 Focal dermal hypoplasia syndrome. There is dysplasia of connective tissue in the skin and skeleton. The irregular, linear, atrophic streaks are present at birth. The dermis is virtually absent.

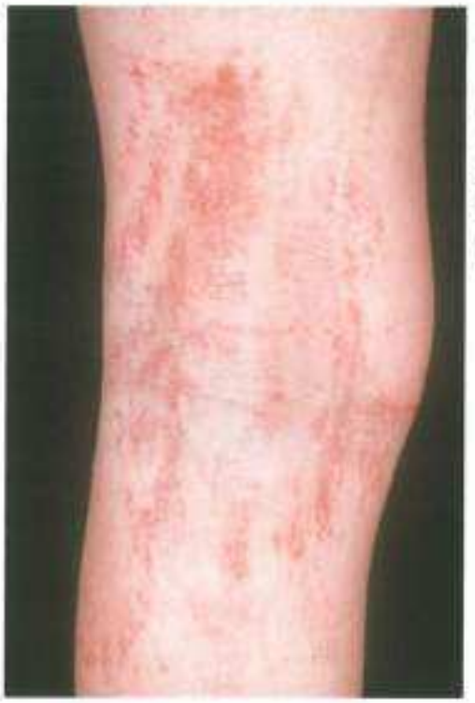


Fig. 20.135 Focal dermal hypoplasia syndrome. Multiple, irregular, erythematous, linear streaks of telangiectasia, atrophy and pigmentation occur on the limbs along Blaschko's lines. (Courtesy of Dr David Atherton.)

Systemic features

Cataracts and hypogonadism occur. These children are small, have a bird-like facies, a small skull and often cataracts and hypogonadism. There is a predisposition to osteosarcoma. Intelligence is usually normal.

Management

There is no treatment other than to protect the skin from ultraviolet irradiation and supervise for cutaneous malignancy.

FOCAL DERMAL HYPOPLASIA SYNDROME

This is a rare multisystem developmental disorder involving all three embryonic layers characterized by virtual loss of the dermis, resulting in linear areas of thinning of the skin following Blaschko's lines with herniation of the subcutaneous fat. It is associated with dental, ocular and asymmetrical skeletal abnormalities including lobster claw deformities of the hand (Goltz syndrome).

Aetiology

It is a rare X-linked or dominantly inherited ectomesodermal condition. There are many different mutations in the *PORCN* gene on Xp11.23, giving rise to highly variable expression. *PORCN* is a member of the porcupine gene family. It encodes a putative O-acyltransferase, which facilitates Wnt protein secretion from the endoplasmic reticulum. Wnt proteins regulate embryonic development by promoting fibroblast proliferation, inhibiting adipogenesis and inducing osteogenesis. It affects both sexes but is usually lethal in males because it is probably inherited as an X-linked dominant and results in miscarriages and stillbirths. There is a profound dysplasia of connective tissue in the skin and skeleton. The collagen fibres are thin and attenuated. The thickness of the dermis is severely reduced and subcutaneous fat is found immediately beneath the epidermis.

Clinical Features

Symptoms

The disorder is present at birth (Fig. 20.134). The skin is sometimes itchy.

Morphology

There are irregular linear streaks (Fig. 20.135) that consist of telangiectasia, cribriform atrophy and pigmentation. The lesions may be hypopigmented in darker skins. There are linear groups of soft, red-yellow nodules, which are herniations of fat at the sites of skin atrophy.

Skin changes vary greatly between patients. Occasionally there is total absence of the skin at birth in severe cases and sometimes the skin atrophy is really quite mild.

Distribution

The trunk and limbs are mainly affected. Multiple papillomas occur on the lips and sometimes the buccal mucous membranes, vulva and anus, rather like raspberries.

The scalp hair is sparse and brittle and the nails are usually small, thin and dystrophic (Fig. 20.136).

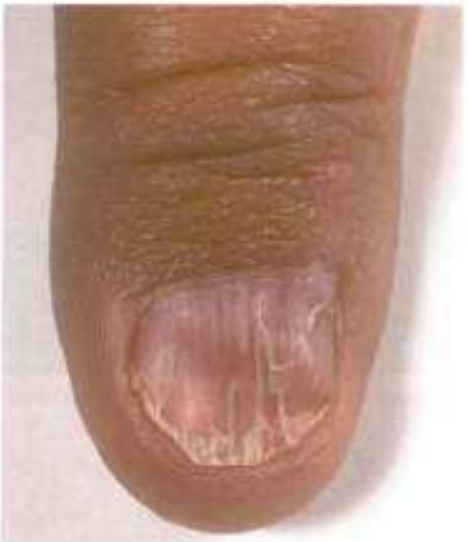


Fig. 20.136 Focal dermal hypoplasia syndrome. The nails are thin and brittle. This syndrome occurs in females, being lethal in males.

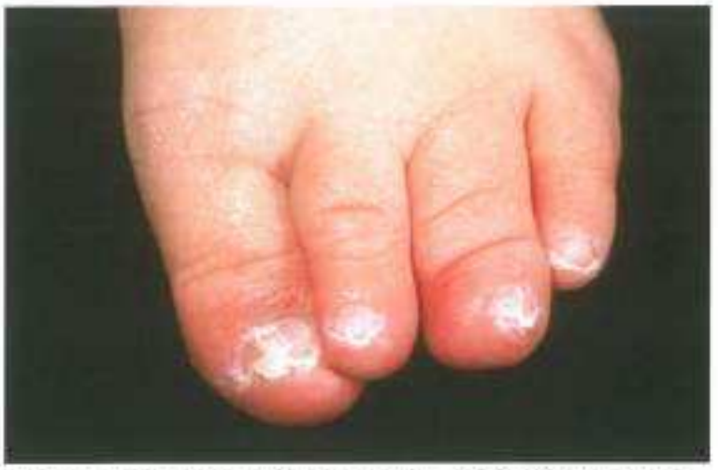


Fig. 20.137 Focal dermal hypoplasia syndrome. Digits may be missing and the nails abnormal. Other abnormalities include short stature, skeletal asymmetry and the lobster claw deformity. (Courtesy of Dr David Atherton.)

Systemic features

There are numerous skeletal abnormalities, in particular short stature, asymmetry of the face, trunk and limbs, and absent (Fig. 20.137), fused or multiple digits, including the lobster claw deformity, which is almost unique to this condition but may be found in the EEC syndrome. There may be oligodontia and peg-shaped teeth, cleft lip and palate and mental retardation. Apocrine tumours (hidrocystomas and apocrine naevi) are frequent.

The head is small, the chin is pointed and the outline of the face is triangular with protruding ears. Ocular colobomas are common.

Management

The linear or reticulate patterning following Blaschko's lines associated with atrophy and telangiectasia makes the diagnosis relatively simple. There is no specific treatment, although lasers have been reported as reducing the telangiectatic component and helping the pruritus. Longitudinal striations of the long bones crossing the epiphyses (*osteopathia striata*) is a helpful radiological sign.

Inherited disorders of connective tissue

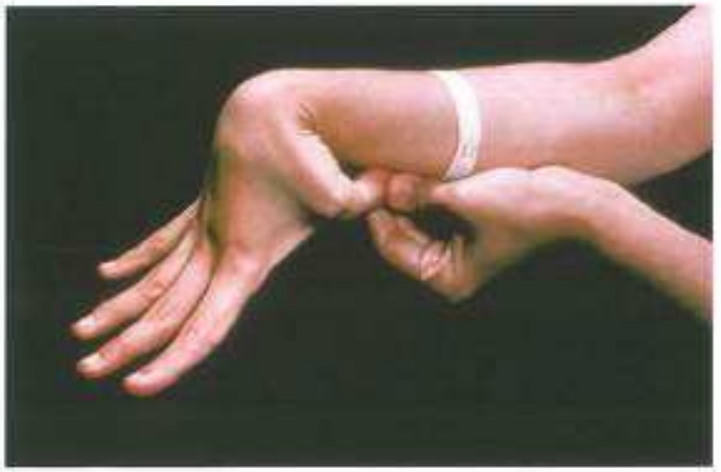
These are a phenotypically diverse group of conditions due to specific mutations in genes encoding various collagens (Ehlers–Danlos syndrome), the components of elastic fibres (cutis laxa) and the ABC cassette membrane transporter (pseudoxanthoma elasticum). They may signify systemic involvement. In *cutis laxa*, there are mutations in *elastin* and *fibulin-5* genes and loss and fragmentation of elastic fibres, resulting in loose sagging skin with little or no elastic recoil (unlike Ehlers–Danlos syndrome), often leading to a progeriatric appearance and systemic manifestations of emphysema, gut and bladder diverticula and umbilical and inguinal hernias.

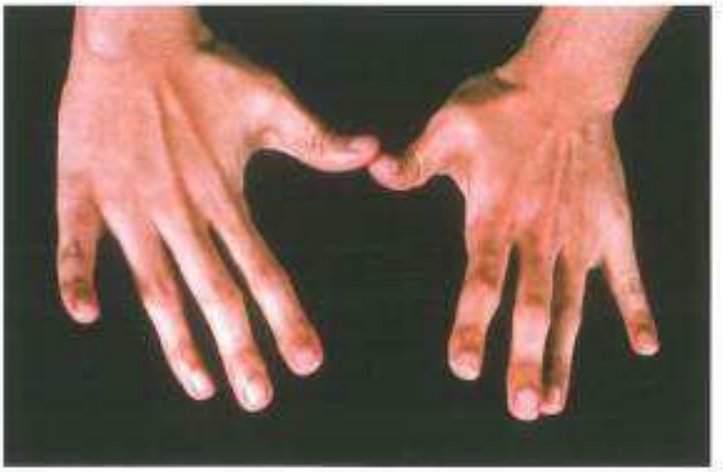
EHLERS–DANLOS SYNDROME

A group of abnormalities of connective tissue biosynthesis that result in soft velvety hyperextensible skin and joints, poor wound healing with cigarette paper scars, easy bruising and in some subtypes, fragility of large blood vessels and viscera.

Aetiology

The molecular basis of most forms has now been elucidated and the syndromes have been reclassified accordingly. The *classic type* (formerly I and II) is an autosomal dominant with hypermobile joints, scoliosis, skin changes, varicose veins, pes planus, mitral valve prolapse and a positive Gorlin's sign (being able to touch the end of the nose with the tongue). There are mutations in *COL5A1* and *2*. The *hypermobility type* (III) is autosomal dominant with generalized joint mobility and extensibility with dislocations leading to chronic pain and osteoarthritis. The skin is smooth and velvety. There is a deficiency of Tenascin X. The *vascular type* (IV) is dominant, has a high risk of rupture of arteries, intestine and the gravid uterus and death. There is a characteristic facies of thin pinch nose, thin lips, hollow cheeks and prominent staring eyes (due to decreased periorbital fat). Mutations in *COL3A1* or haplo-insufficiency of type III collagen cause abnormal type III collagen. The *kyphoscoliotic type* (VI) is autosomal recessive, is characterized by progressive kyphoscoliosis, generalized joint laxity, scleral laxity (leading to rupture of the ocular globe), variable skin changes and severe loss of muscle tone at birth ('floppy baby'), causing serious motor dysfunction.





Figs 20.138 and 20.139 Ehlers–Danlos syndrome. The joints are hyperextensible and dislocate easily. (Courtesy of St Mary's Hospital.)

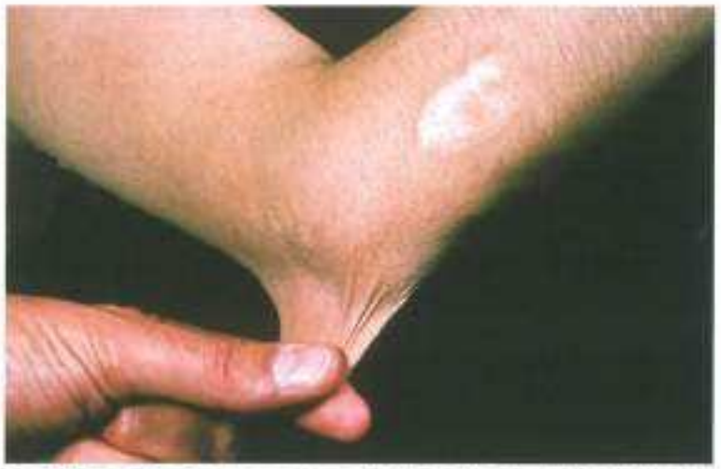


Fig. 20.140 Ehlers–Danlos syndrome. The skin is soft, velvety, fragile (note scar) and hyperextensible. Histopathologically the dermal collagen is scanty, whorled and disorderly. The elastic fibres are abnormal. (Courtesy of St Mary's Hospital.)

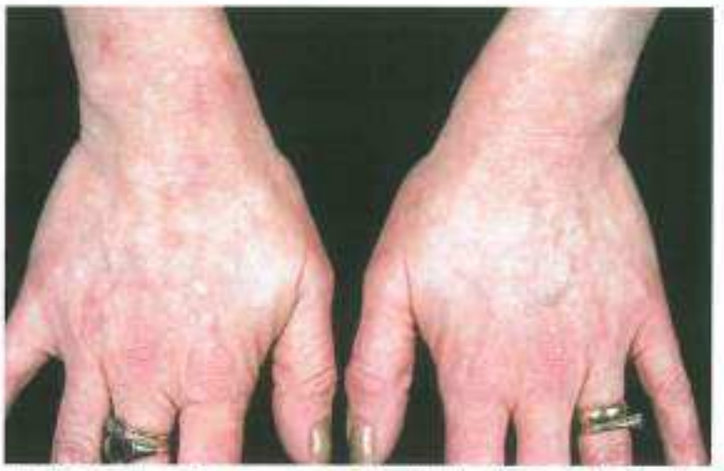


Fig. 20.141 Ehlers–Danlos syndrome. The skin is thin, translucent and fragile. In type IV, bruising and premature ageing predominate without hyperextensibility of the skin and with limited joint hypermobility. It is associated with spontaneous rupture of large arteries, the colon and the gravid uterus.

There are mutations in the *PLOD1* gene (procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1), which cause lysyl hydroxylase deficiency and abnormal cross-linking profile. The *arthrochalasia type* (VII A and B) is autosomal dominant and characterized by joint hypermobility, recurrent subluxations, congenital hip dislocations, hypotonia, kyphoscoliosis and skin changes. *COL1A1* and 2 are mutated. The *dermatosparaxis type* (VII C) is a recessive. There is marked skin fragility with sagging redundant skin and a distinctive facies with puffy eyelids, micrognathia and blue sclerae. The teeth are abnormal with gingival hyperplasia. The limbs are short and there are large umbilical and inguinal herniae and premature rupture of the fetal membranes. *ADAMTS2* is mutated leading to thin collagen fibrils. The others (formerly V, VIII and X) are not classified at present because their clinical features are not distinctive enough and their molecular explanation unknown.

Clinical Features

Symptoms

Easy bruising, poor healing, joint hypermobility (Figs 20.138 and 20.139) and other symptoms depend on the type; symptoms are usually apparent early in life.

Morphology

The conditions have in common hyperelastic skin (Fig. 20.140) that recoils immediately to its normal position (which it does not in cutis laxa). Subsequently, the skin may become pendulous. The skin over the palms and soles tends to be loose and redundant. The skin is thin, fragile, soft and velvety (Fig. 20.141). It splits and tears easily. It is difficult to suture because of this and it is best to tape cutaneous wounds. Healing is poor and tissue paper scars form (Fig. 20.142). Herniations of fat through the dermis are common, particularly over the knees and elbows, and are known as molluscoid pseudotumours.

Management

There is no specific treatment. The identification of the exact defect is valuable for genetic counselling.

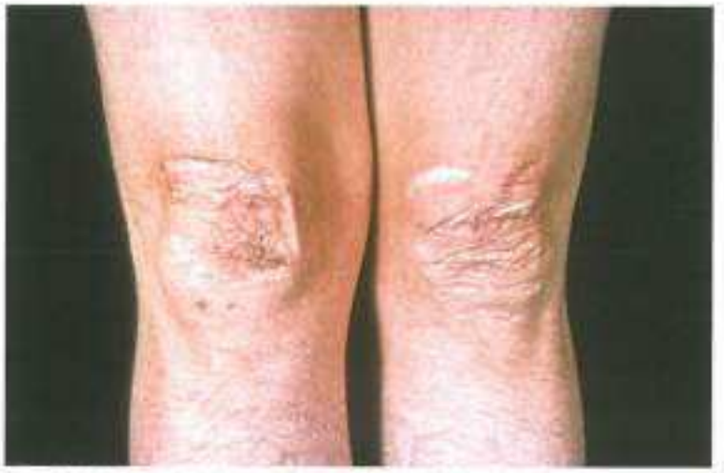


Fig. 20.142 Ehlers–Danlos syndrome. The skin is fragile and heals poorly with unsightly scars. (Courtesy of St Mary's Hospital.)

PSEUDOXANTHOMA ELASTICUM

A rare set of inherited disorders characterized by a generalized disturbance of elastic tissue in the dermis, large blood vessels and Bruch's membrane.

Aetiology

The condition is phenotypically diverse, because there are many different mutations in the *ABCC6* (adenosine triphosphate-binding cassette subfamily C, member 6) gene, which encodes MRP6, an ATP-binding cassette protein serving as a putative trans-membrane transporter. It is thought that this results in an accumulation of substances with an affinity for elastin fibres, which clump and become distorted and then calcium is deposited. It is inherited as an autosomal recessive. Histologically, clumped, degenerate, fragmented, swollen, elastic fibres are found in the mid-dermis and calcium accumulates within them. The collagen fibres are also abnormal. Occasionally, transepidermal elimination of the abnormal elastic fibres may occur. Clinical manifestations vary and the skin may appear normal but a biopsy should demonstrate these abnormalities.

Fig. 20.143 Pseudoxanthoma elasticum. Soft yellow papules resembling 'plucked chicken skin' occur at the sides of the neck and in the elbow flexures.

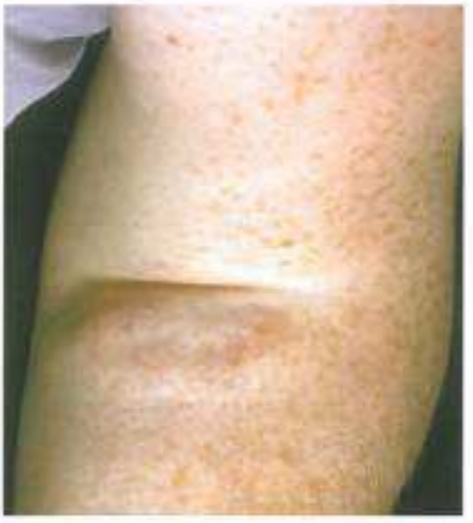


Fig. 20.144 Pseudoxanthoma elasticum. Soft, yellow, loose, thickened skin occurs in the elbow flexures.

Fig. 20.145 Pseudoxanthoma elasticum. The skin is soft, loose and thickened. The sides of the neck are characteristically involved. (Courtesy of the late Dr R. H. Marten.)

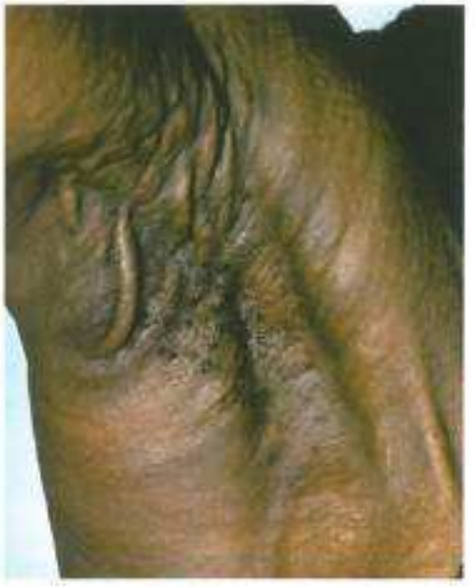


Fig. 20.146 Pseudoxanthoma elasticum. The skin may hang down in folds. The axillae are typically involved. (Courtesy of the late Dr R. H. Marten.)

Fig. 20.147 Pseudoxanthoma elasticum. Angioid streaks are wider than blood vessels and extend radially across the fundus away from the optic disc. They are characteristic and caused by cracking of Bruch's membrane.

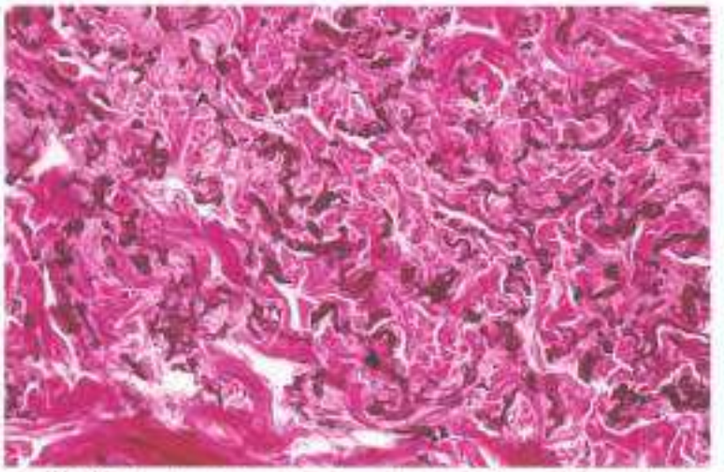


Fig. 20.148 Pseudoxanthoma elasticum. Irregular, thickened, fragmented elastic fibres occupy the middle and lower dermis in a haphazard manner.

Clinical Features

Symptoms

The cutaneous abnormalities are usually evident before adolescence.

Morphology

Soft yellow papules (Fig. 20.143) are arranged in a linear or reticular manner and form plaques (Fig. 20.144). The skin is soft, lax and slightly wrinkled and gradually becomes loose and thickened (Fig. 20.145) with a pebbled appearance. The skin ultimately may hang in folds.

Distribution

The neck, axillae (Fig. 20.146), groins, umbilicus and antecubital and popliteal fossae are usually involved.

Systemic features

Angioid streaks in the eyes (Fig. 20.147), caused by the cracking of Bruch's membrane, are characteristic, but do occur in other conditions such as thalassaemia, sickle cell disease, Paget's disease of bone and lead poisoning. These are wider than blood vessels and extend radially across the fundus, away from the optic disc. They usually occur after 20 years of age and result in neovascularization, haemorrhage and visual impairment.

The elastic tissue in the media and intima of the larger arteries and those supplying the viscera, mesentery and the extremities become involved. Calcification leads to vascular occlusion. Angina, renal hypertension, cerebrovascular accidents and gastrointestinal and urinary tract haemorrhage may occur.

Management

A skin biopsy (Fig. 20.148) and gene analysis help to confirm the diagnosis. Laser photocoagulation may prevent retinal haemorrhage and careful vascular assessment may prevent complications. Similar skin lesions may be induced by D-penicillamine. There is no specific treatment.

Connective tissue disorders 21

Lupus erythematosus

A spectrum of autoimmune disorders ranging from a localized photosensitive skin eruption to a potentially fatal multisystem disease, with a subacute cutaneous variety in between associated with immunological abnormalities including antibodies to nuclear materials.

Aetiology

Lupus erythematosus (LE) is a chronic autoimmune disorder influenced by genetic, environmental (smoking and ultraviolet irradiation) and hormonal factors. It occurs in all races and is more common in women, but presentations differ. Afro-Caribbean/African-American females have a fourfold risk over Caucasian women and nephritis is a serious complication, but photosensitivity is less common. LE may be acute and systemic, subacute or chronic.

Systemic LE affects the lungs, the central nervous system, the joints and the kidneys (which frequently determines the outcome). Fatigue is characteristic, while fever, lymphadenopathy, haemolytic anaemia, leukopenia and thrombocytopenia are common. It runs a remitting and relapsing course and may be precipitated by strong sunlight, infection, physical or mental stress, menstruation, trauma and drugs. Various antibodies have been demonstrated, particularly to nuclear material and to DNA. Hypocomplementaemia, hypergammaglobulinaemia, positive rheumatoid factor, positive Wasserman reactions and LE cells are other abnormal immunological findings. The American Rheumatism Association has produced criteria based on these abnormalities that act as guidelines in establishing the diagnosis. If the patient has, or has had, four or more of the criteria, systemic LE is considered likely:

- Photosensitive rash, oral ulcers
- Arthritis and arthralgias
- Serositis (pleuritis and pericarditis)
- Nephropathy (proteinuria/cellular casts)
- Seizures/psychosis
- Haemolytic anaemia
- Leucopenia/lymphopenia/thrombocytopenia
- Positive anti-DNA, anti-Sm, antinuclear antibodies and antiphospholipid antibodies
- False-positive syphilis serology
- Other suggestive features are xerophthalmia, vasculitis and Raynaud's.

Subacute LE (SCLE) was described by Sontheimer in 1979. The lesions are psoriasiform and/or annular. Photosensitivity is marked. Systemic features are mild or absent. Raynaud's phenomenon, mucous membrane ulceration and cutaneous vasculitis are common. It particularly afflicts young women, peaking in the mid-forties. Anti-Ro/SSA antibodies are positive and direct skin immunofluorescence shows particulate epidermal staining. HLA-DR3 is often positive.

Chronic discoid LE is localized and occasionally generalized. Systemic features and autoantibodies are rare. There is particulate dermal-epidermal junction staining with immunofluorescence. The dermal infiltrate is deeper than in SCLE. Non-specific vascular lesions occur, which may affect the skin, particularly leucocytoclastic vasculitis, thrombophlebitis and livedo reticularis. Livedo reticularis with ischaemic CNS disease is known as *Sneddon's syndrome* and with antiphospholipid antibodies as *Hughes' syndrome*. Erythema multiforme-like lesions, which may be associated with acute or subacute LE, is known as *Rowell's syndrome*.

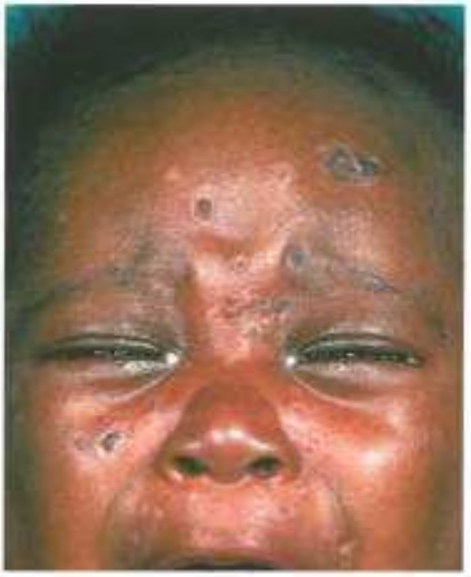


Fig. 21.1 Lupus erythematosus. This infant's mother had anti-Ro and La-positive systemic lupus erythematosus. The importance of diagnosis at birth is the identification and treatment of the heart block that may accompany it. (Courtesy of Dr Elisabeth Higgins.)

There is a rare *neonatal variant* with a transient lupus dermatitis on the face (Fig. 21.1) associated with an isolated complete permanent congenital heart block. There is a high frequency of anti-Ro (SSA) and anti-La (SSB) antibodies in their mothers, from whom they passively acquire the antibody. The heart block develops from the 18th week of gestation and the infants require a pacemaker. Consequently, babies with mothers with anti-Ro antibodies require regular ultrasound fetal heart monitoring. The mothers may be asymptomatic or have sicca syndrome, photosensitivity and arthralgias.

Cutaneous LE may also be associated with complement deficiencies, particularly C2 deficiency inherited as an autosomal recessive gene on the short arm of chromosome 6. There are extensive, non-scarring, photosensitive, scaly patches with no or low antinuclear factors and minimal if any renal involvement. Arthralgias are not uncommon. The CH_{50} (dose of complement giving 50% haemolysis) is reduced and there are usually positive anti-Ro antibodies. Recurrent pyogenic infections as a result of impaired bacterial opsonization and lysis are common. Although commonly associated with LE, other connective tissue disorders may sometimes be associated.

DISCOID LUPUS ERYTHEMATOSUS

Clinical Features

Symptoms

There is a facial rash often precipitated by sunlight.

Morphology

Well-defined, disc-like plaques (Fig. 21.2) are initially red, raised and sometimes mauve (Fig. 21.3), purpuric or oedematous. There is tenacious scaling, hyperkeratosis and follicular plugging (Fig. 21.4). Healing follows centrally, sometimes with scarring (which in the scalp leads to permanent loss of hair). The margin of the plaque is often hyperpigmented, while centrally there may be depigmentation.

Distribution

Light-exposed areas are most affected, particularly the cheeks (Fig. 21.5), nose (Fig. 21.6), forehead, back of hands (Fig. 21.7) preauricular area (Fig. 21.8), ears and scalp (Fig. 21.9). Sometimes the lips and occasionally the inside of the mouth are involved (Figs 21.10 and 21.11).

Cutaneous involvement may be more widespread (Fig. 21.12) (*generalized discoid LE*), with a slightly increased risk of systemic involvement.

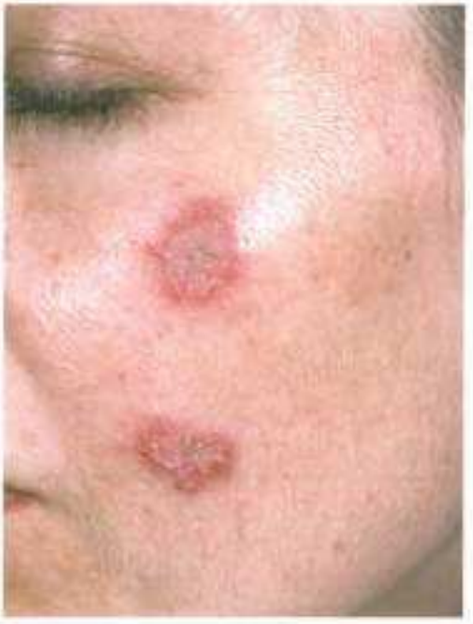


Fig. 21.2 Discoid lupus erythematosus. Very well-defined disc-like plaques that are red and have a thick scale occur over the cheeks.

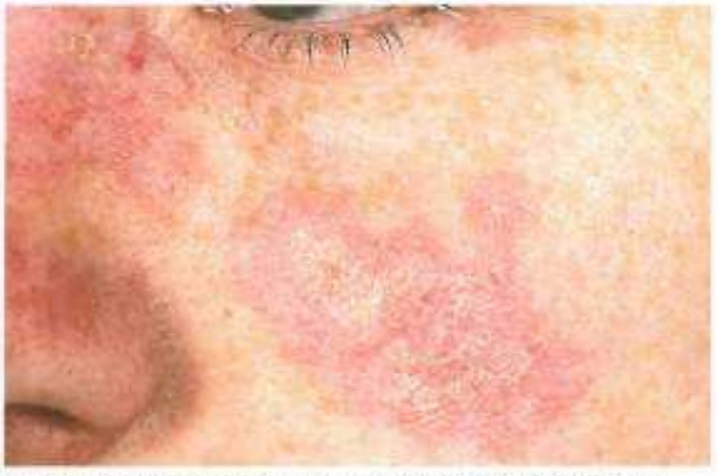


Fig. 21.3 Discoid lupus erythematosus. Light-exposed areas such as the cheeks are particularly affected. The mauve colour is quite characteristic.

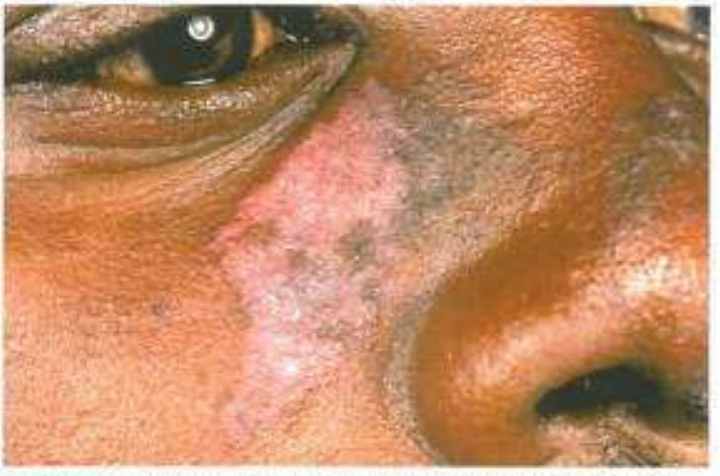


Fig. 21.4 Discoid lupus erythematosus. Follicular plugging is visible on the nasal side of the plaque. This characteristic is also seen histologically.

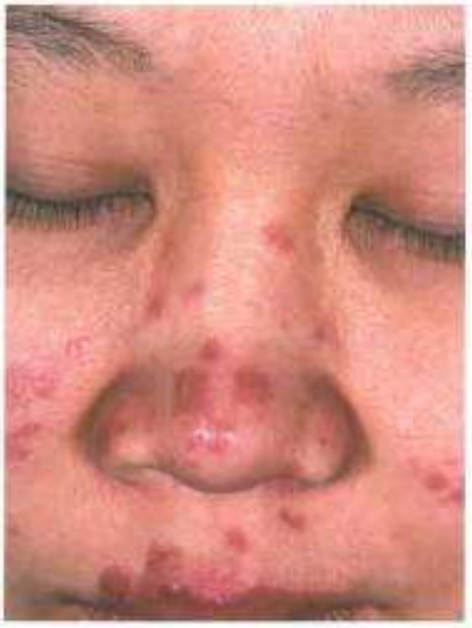


Fig. 21.5 Lupus erythematosus. The skin lesions are often precipitated by sunlight and occur in a butterfly distribution over the cheeks and nose.

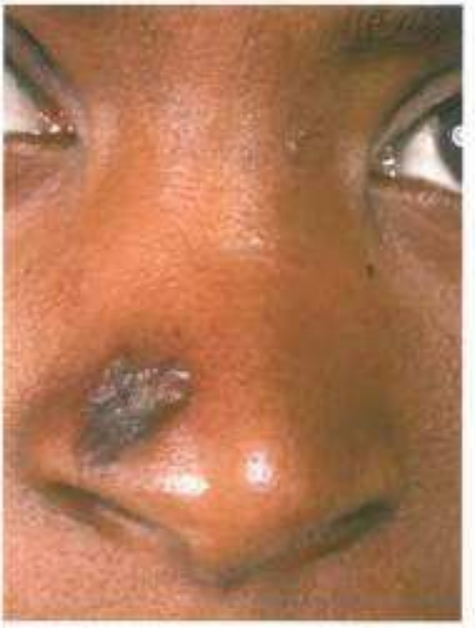


Fig. 21.6 Discoid lupus erythematosus. The plaques are well defined, red and have a tenacious scale. Scarring and hyperpigmentation result. A biopsy will prove the diagnosis.

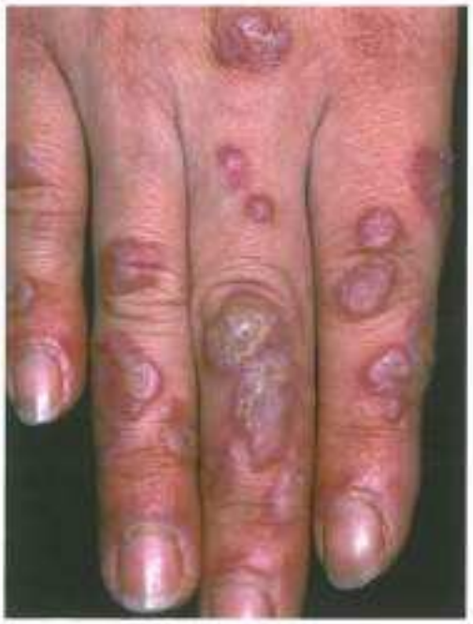


Fig. 21.7 Lupus erythematosus. Light-exposed skin is involved in photodermatoses. There are well-defined purple plaques with a tenacious scale on the backs of the hands in this patient with discoid lupus erythematosus.

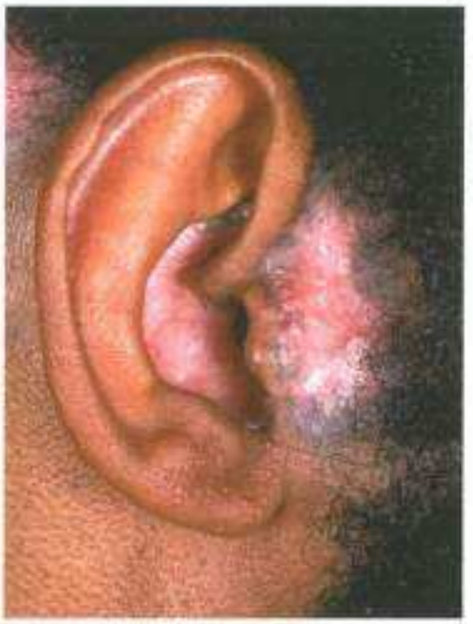


Fig. 21.8 Discoid lupus erythematosus. There are well-defined, erythematous, scaling lesions with a pigmented margin and hair loss in front of and behind the ear in this West Indian.

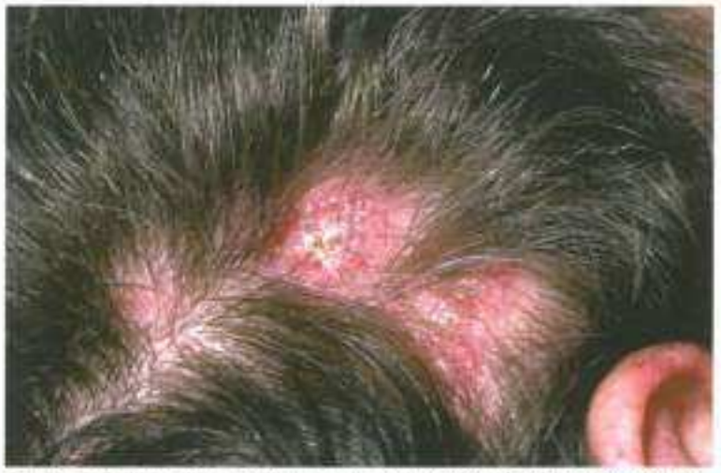


Fig. 21.9 Discoid lupus erythematosus. In the scalp, there is complete loss of hair with erythema and adherent scaling.

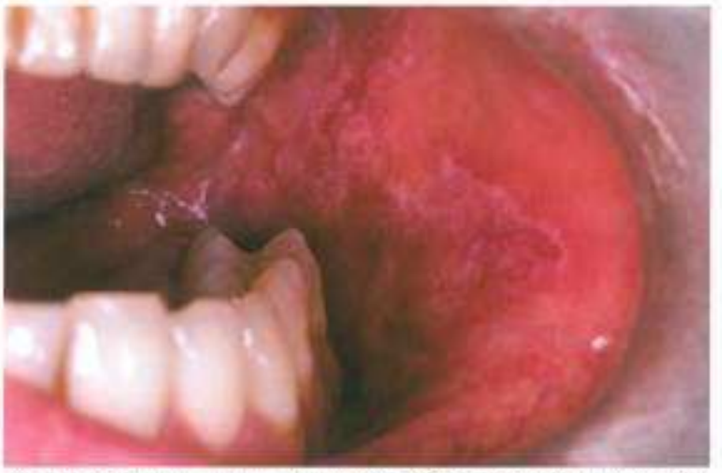


Fig. 21.10 Oral lupus erythematosus. Well-defined discoid plaques may occur in the mouth. Biopsy is necessary to establish the diagnosis.

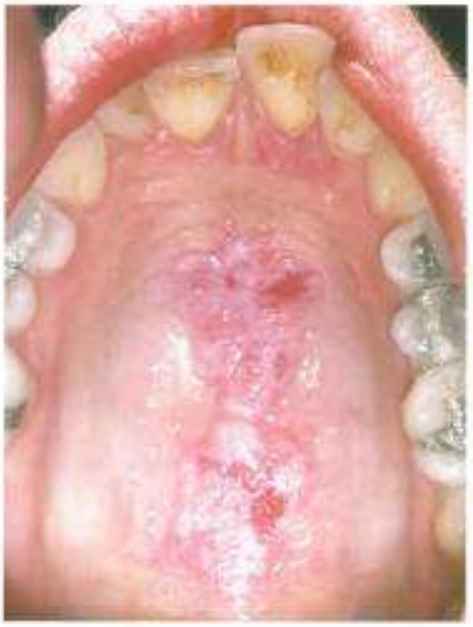


Fig. 21.11 Oral lupus erythematosus. There are well-defined whitish plaques which have become eroded. A biopsy is required for precise diagnosis.

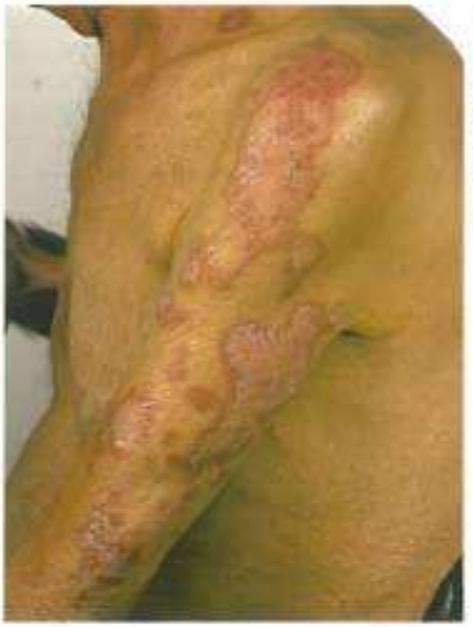


Fig. 21.12 Widespread chronic discoid lupus erythematosus. Biopsy is required to distinguish this from psoriasis. There is a slight risk of systemic involvement in these patients. This patient is also jaundiced.

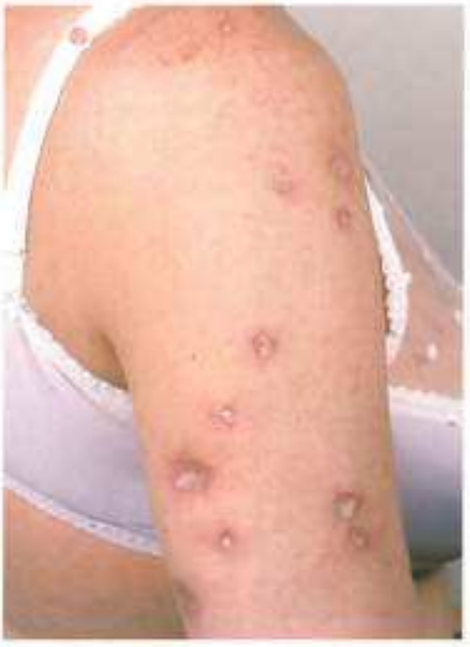


Fig. 21.13 Lupus erythematosus profundus. Destructive subcutaneous atrophy results from lupus in the deep dermis and subcutis. (Courtesy of the late Dr R. H. Marten.)

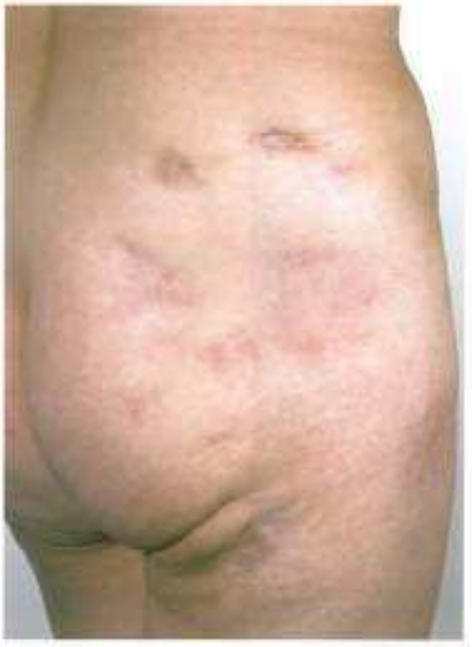


Fig. 21.14 Lupus erythematosus profundus. The buttocks are a characteristic site for this variant.

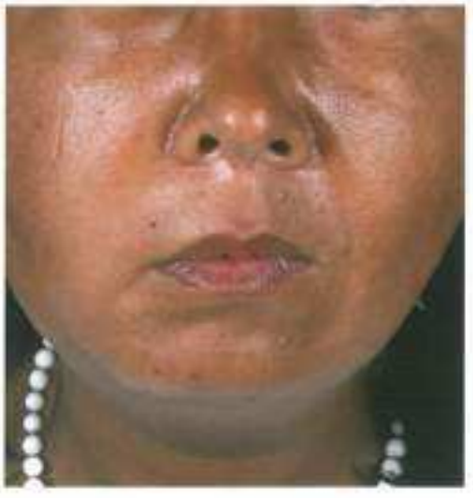


Fig. 21.15 Lupus erythematosus profundus. This is rare. One side of the face is oedematous and sclerodermatous. The antinuclear antibody was positive at 1/40 only.

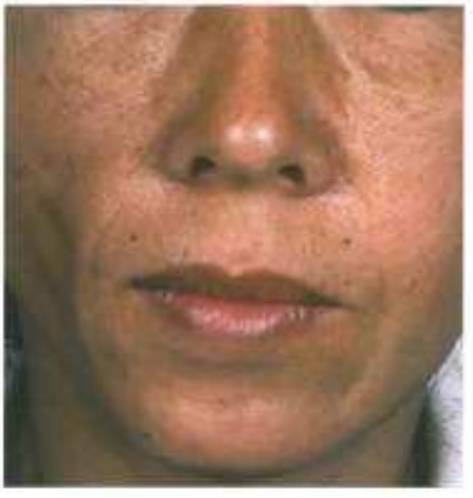


Fig. 21.16 Lupus erythematosus profundus. It responded to systemic steroids and antimalarial drugs, but with disfiguring atrophy. In 13 years of follow-up there have been no systemic features.

Variants of chronic LE are:

- *LE profundus.* The deep dermis and subcutis are affected, such that nodules occur. The limbs (Fig. 21.13) and buttocks (Fig. 21.14) are usual sites. Destructive subcutaneous atrophy results (Figs 21.15 and 21.16).
- *Hypertrophic discoid LE.* The lesions are rather verrucous and hyperkeratotic (Fig. 21.17) but occur in association with ordinary LE, which aids the diagnosis. Histologically there may be a mixture of features of LE and lichen planus.
- *Lupus tumidus* (Fig. 21.18)
- *Lupus panniculitis*
- *Chilblain lupus.*

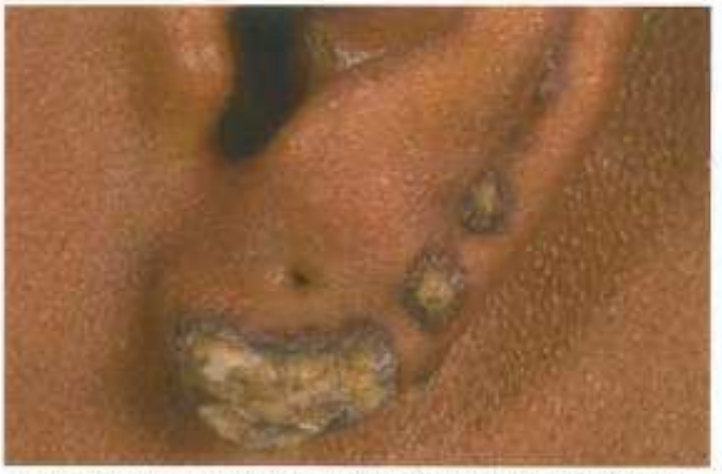


Fig. 21.17 Verrucous lupus erythematosus. An unusual variant is warty and hypertrophic and can occur in association with more typical lupus erythematosus.

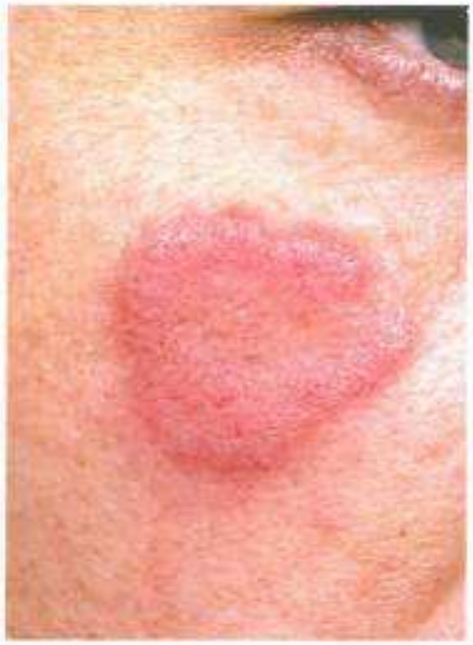


Fig. 21.18 Lupus erythematosus tumidus. The lesions may be quite red and oedematous. 'LE tumidus' is a highly photosensitive subtype, which resolves with systemic steroids and antimalarial drugs without scarring and pigmentation.

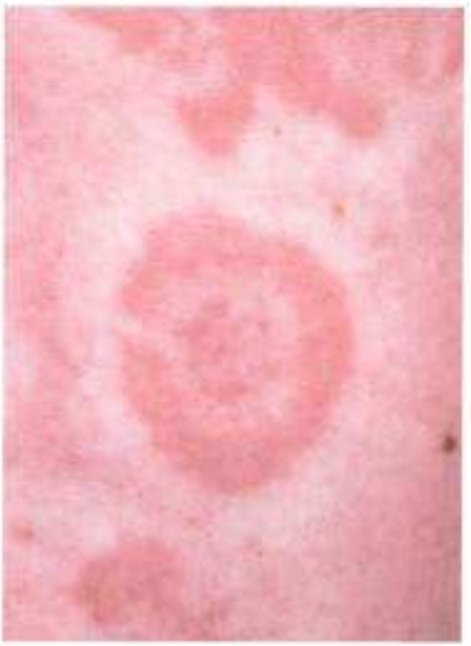


Fig. 21.19 Subacute lupus erythematosus. The lesions are red, raised and often annular. Scarring and follicular plugging are usually absent. Anti-Ro (SSA) antibodies are present in all patients.

SUBACUTE LUPUS ERYTHEMATOSUS

Clinical Features

Symptoms

Pronounced photosensitivity, usually in young white women.

Morphology

There is no scarring or follicular plugging. The lesion may be symmetrical annular (Fig. 21.19) or papulosquamous. Telangiectasia may be prominent. Although hyper- or hypopigmentation may occur as the lesions fade, there is ultimately no residual change.

Distribution

The eruption is more photosensitive than discoid cutaneous LE, involving the face, shoulders, upper back, extensor aspects of arms, feet and the 'V' of the front of the chest (Figs 21.20 and 21.21). Diffuse non-scarring alopecia may occur.

Systemic Features

There may be mild musculoskeletal abnormalities, but neurological and renal involvement is rare. Antinuclear antibodies (ANA) C_2/C_4 deficiency, rheumatoid factor, circulating immune complexes, lymphopenia and thrombocytopenia are commonly found. Anti-SSA/Ro antibodies are positive in 100% of patients (Ro antibodies are also positive in Sjögren's, chilblain and neonatal LE). Direct immunofluorescence of normal skin is positive in about a quarter. Carriers of *HLA-B8* and *HLA-BR3* alleles are particularly prone to this variety.

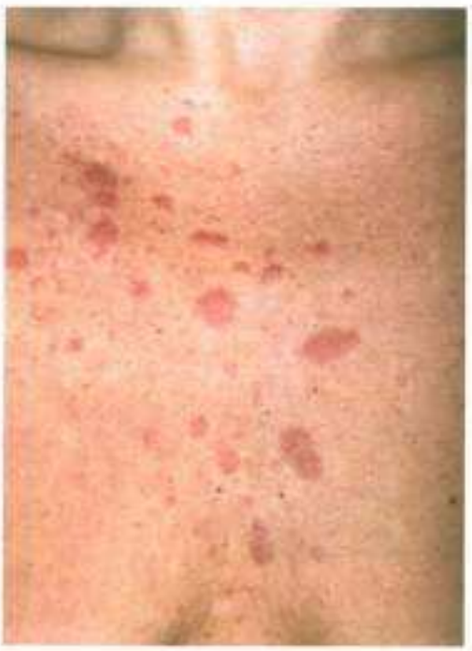


Fig. 21.20 Subacute lupus erythematosus. The lesions are more extensive than in discoid lupus erythematosus but retain a photo-exposed distribution, such as the front of the chest.

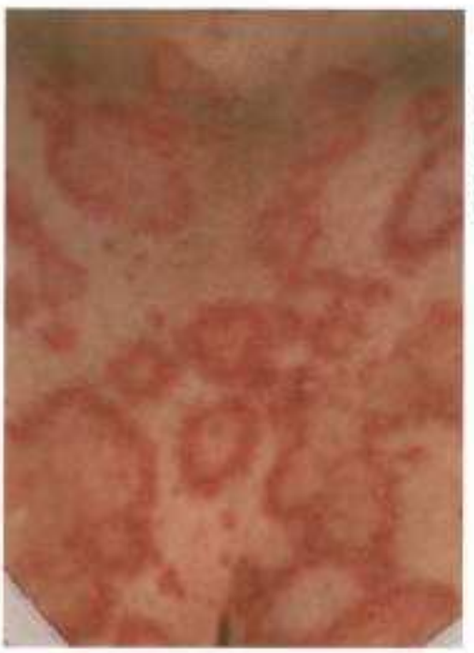


Fig. 21.21 Subacute lupus erythematosus. The annular configuration of the lesion is clearly demonstrated. There may be mild musculoskeletal abnormalities but neurological and renal damage is rare.

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Features

Symptoms

A photosensitive rash may or may not be present.

Morphology

There are a variety of manifestations:

- identical to that of chronic discoid LE
- a mauve erythema (Fig. 21.22) over the cheeks and bridge of the nose (so-called 'butterfly rash') that heals without scarring
- a more widespread maculopapular eruption on light-exposed areas (Fig. 21.23), particularly the face, neck (Fig. 21.24) and the arms
- *chilblain lupus* (Fig. 21.25)
- a vasculitis that affects the extensor surfaces of the forearms, dorsa of the hands, small joints of the fingers, palms (Fig. 21.26) and periungual skin

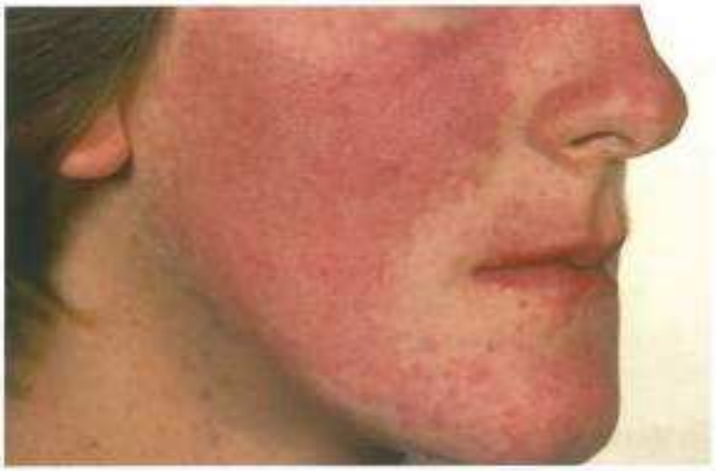


Fig. 21.22 Systemic lupus erythematosus. A diffuse blotchy erythema is present on the face, particularly over the cheeks and nose.

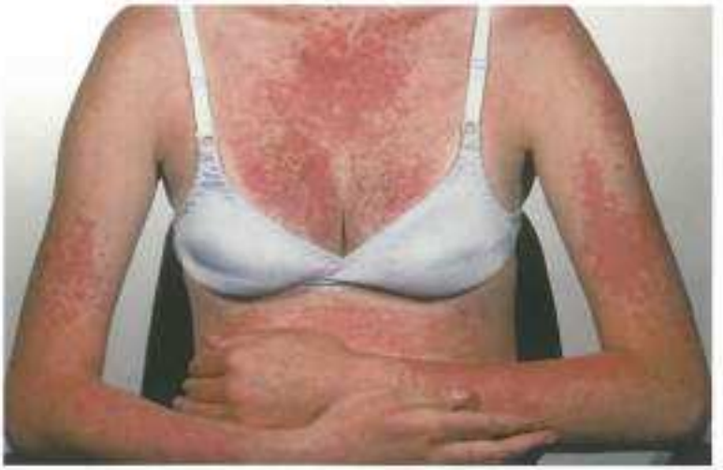


Fig. 21.23 Systemic lupus erythematosus. The distribution is that of photosensitivity. This is the same patient as in Fig. 21.22.

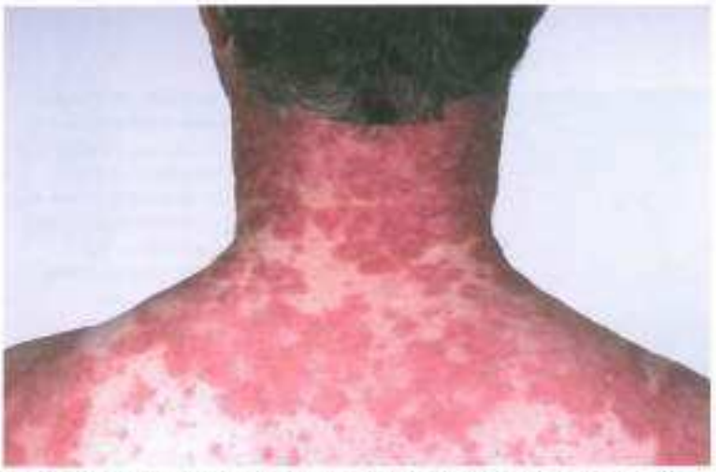


Fig. 21.24 Systemic lupus erythematosus. Infection and ultraviolet light are common precipitants of lupus erythematosus but alcohol misuse was the cause here.

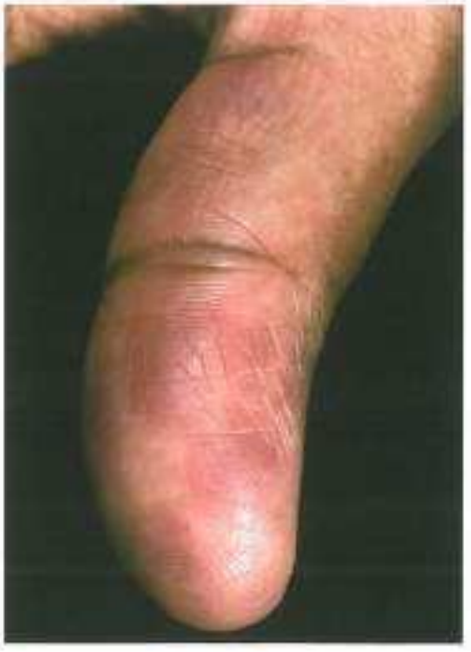


Fig. 21.25 Chilblain lupus erythematosus. Painful purple plaques occur on the fingers in response to cold. This woman's antinuclear antibody was 1/1250.

- a diffuse alopecia (Fig. 21.27), which indicates active disease. The hair regrows as the disorder remits
- Raynaud's phenomenon
- thrombophlebitis
- livedo reticularis
- urticarial eruptions are among the non-specific cutaneous manifestations
- blistering (Fig. 21.28) from photosensitivity (*bullous LE of childhood*).

Distribution

Photosensitive areas.

Systemic features

Fatigue, recurrent low-grade fever, joint pains, diffuse non-scarring hair loss, photosensitivity and Raynaud's phenomenon. Lymphadenopathy, unexplained anaemia, leucopenia, cutaneous vasculitis, pleurisy and the presence of autoantibodies.

Management of Lupus Erythematosus

The exact diagnosis is based on the cutaneous findings, the degree, if any, of systemic disturbance, skin biopsy, immunofluorescent studies and a search for autoantibodies. Histologically, in discoid LE there is hyperkeratosis, follicular plugging (Fig. 21.29) and epidermal atrophy. Basal cell

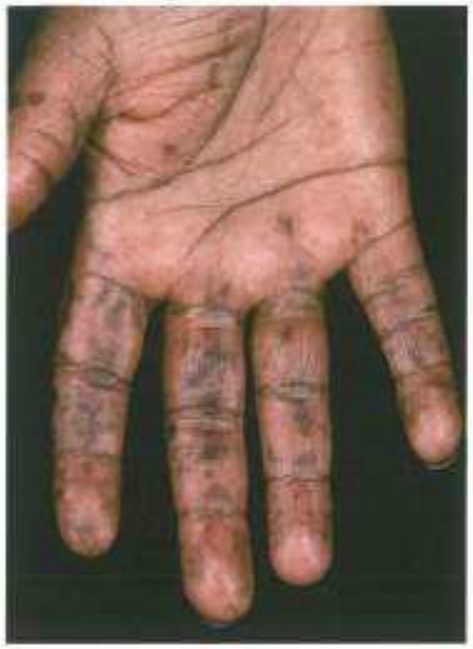


Fig 21.26 Systemic lupus erythematosus. The palms are frequently involved in systemic lupus erythematosus. Postinflammatory hyperpigmentation is common in black skins.

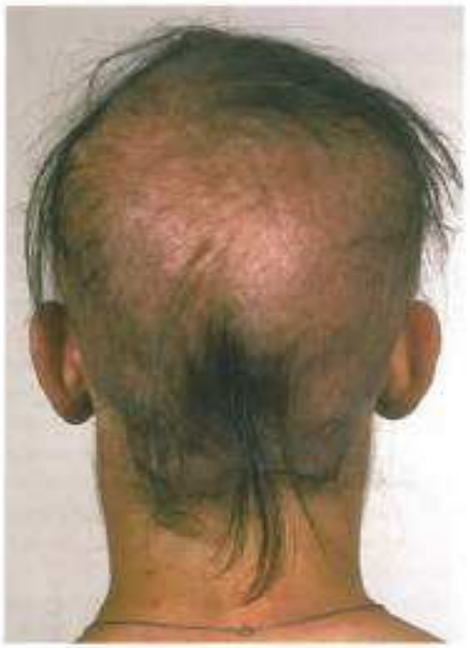


Fig. 21.27 Systemic lupus erythematosus. A diffuse alopecia is common in systemic disease and is an indicator of active disease.

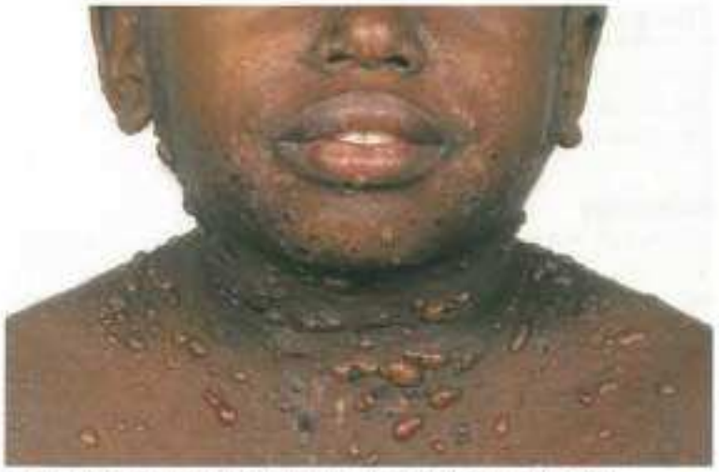


Fig. 21.28 Bullous lupus erythematosus of childhood. This is rare. The blisters were induced by ultraviolet irradiation. Autoantibodies and skin immunofluorescence were positive and there was nephritis.

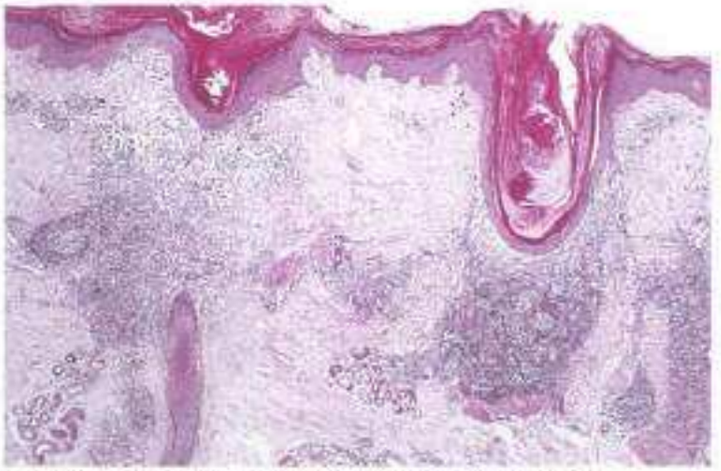


Fig. 21.29 Discoid lupus erythematosus. A low-power view shows hyperkeratosis, conspicuous follicular plugging and a periadnexal heavy chronic inflammatory cell infiltrate.

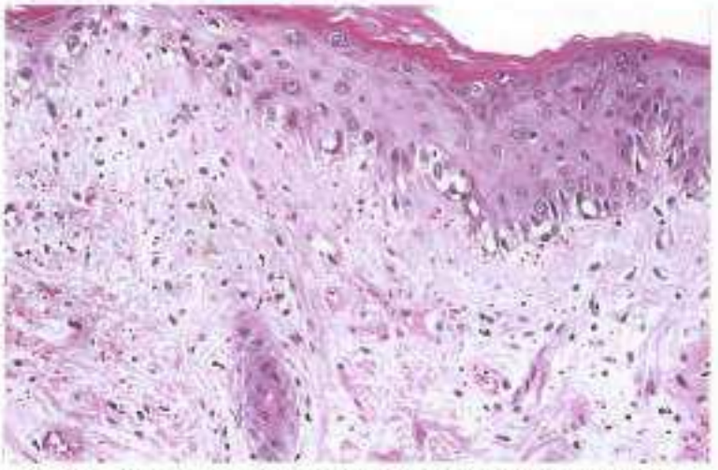


Fig. 21.30 Discoid lupus erythematosus. Basal cell hydropic degeneration is marked. Epidermal atrophy is present. There are extravasated red cells in the dermis.

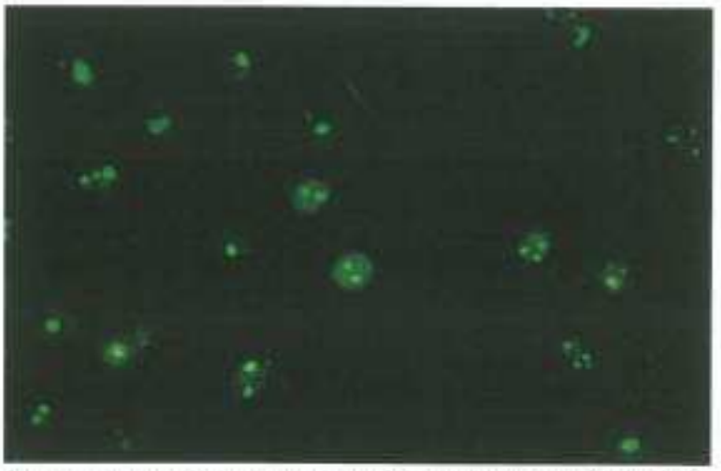


Fig. 21.31 Antinuclear antibodies. These antibodies are demonstrated here by using HEP2 cells (x500). (Courtesy of Dr M. Snaith.)

hydropic degeneration (occasionally associated with cytoid body formation) is characteristic (Fig. 21.30) and pigmentary incontinence is usually evident. The basement membrane is commonly thickened. A perivascular and periadnexal chronic inflammatory cell infiltrate is a diagnostic feature. Telangiectasia is frequently present. In subacute cutaneous LE, parakeratosis is often a feature and the epidermis may be variably acanthotic or atrophic. Inter- and intraepidermal oedema is often present and satellite cell necrosis is a diagnostic pointer. Marked basal cell hydrophic degeneration is characteristic. A superficial lichenoid infiltrate with perivascular accentuation is usually evident. Systemic LE may mimic the discoid variant but more often is histologically rather bland, comprising focal mild basal cell hydropic degeneration, superficial dermal oedema and a mild perivascular chronic inflammatory cell infiltrate.

A thick band of immunoglobulin (IgG) is deposited along the dermoepidermal junction, which ultrastructurally is on the upper dermal collagen fibres and along the lamina densa. There is a similar band on direct immunofluorescence staining in clinically normal skin in extracutaneous disease (positive lupus band test).

As a general rule, all ANAs are negative (or minimally positive) in discoid LE, to some degree positive in subacute LE and strongly positive (Fig. 21.31) in systemic LE. The ANAs are usually homogeneous or particulate. Antibodies to native or double-stranded DNA are usually associated with significant lupus nephritis. High titres of antibodies to double-stranded DNA are fairly diagnostic of systemic LE. Antibodies to single-stranded DNA are also found but are less specific, and antibodies to extractable nuclear antigens (ENAs) occur in mixed connective tissue disease. In subacute LE, although ANAs are present, antibodies to double-stranded DNA are relatively uncommon but antibodies to Ro/SSA are common. Peripheral staining is indicative of active systemic LE and is associated commonly with nephritis. Antibodies to histones suggest a drug-induced LE.

In active disease, the erythrocyte sedimentation rate (ESR) is raised, there is a polyclonal hypergammaglobulinaemia and serum complement levels are usually diminished. The Wasserman reaction and rheumatoid factor may be positive. LE cells are usually present. These are demonstrable when serum is incubated with normal neutrophils.

Management depends upon the severity of the disease. Systemic corticosteroids may be life saving in systemic disease but are not indicated in the average patient with discoid LE. Precipitating factors, such as ultraviolet light, should be avoided and photoprotective sunscreens used. Smoking is a significant factor in cutaneous LE in the genetically predisposed. It is thought to have a phototoxic and immunomodulatory effect. Antimalarials are also inactivated by cigarettes. Cold weather should be prepared for with warm clothing and central heating. Medications that are known to exacerbate the disease, such as sulphonamides or pyrazolones, should not be used. Pregnancy and oral contraceptives may exacerbate the systemic disease.

Superpotent corticosteroids are helpful for chronic discoid lesions. Antimalarial drugs may benefit more widespread lesions, particularly chloroquine and mepacrine. The former can cause retinal damage and the eyes should be monitored. Mepacrine causes a yellow pigmentation of the skin. Immunosuppressives, such as azathioprine, may have a steroid-sparing effect in systemic disease. Rituximab is increasingly being used, but there have been reports of JC virus-induced leuco-encephalopathy. However, systemic steroids remain the mainstay of therapy for these patients.

The antiphospholipid syndrome

A syndrome comprising livedo reticularis, recurrent miscarriages, venous and arterial thromboses and occasionally thrombocytopenia associated with autoantibodies against endogenous phospholipids.

Aetiology

Antiphospholipid antibodies are a heterogeneous group of circulating antibodies against negatively charged phospholipids. Cardiolipin is the phospholipid most commonly used, but it should be noted that reagin (the first antibody to be used against cardiolipin, in the diagnosis of syphilis) produces biologically false-positive results. Subsequently, it has been shown that anticardiolipin antibodies and a lupus anticoagulant are associated with a distinct ANA-negative syndrome of arterial and venous thromboses including involvement of the placenta, leading to recurrent spontaneous fetal loss, particularly in the second trimester. The lupus anticoagulant is an antiphospholipid antibody that inhibits phospholipid-dependent coagulation assays and should be suspected in the presence of an unexplained prolonged activated partial thromboblastin time. However, despite in vitro clotting prolongation suggesting a bleeding diathesis, these patients have recurrent thromboses. The condition may

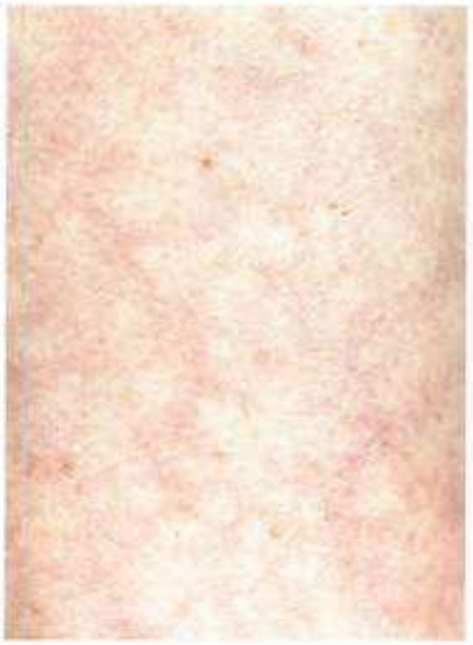


Fig. 21.32 Livedo reticularis. A mauve net-like discoloration on the limbs associated with recurrent miscarriages, venous and arterial thromboses and thrombocytopenia are suggestive of the anticardiolipin antibody syndrome.

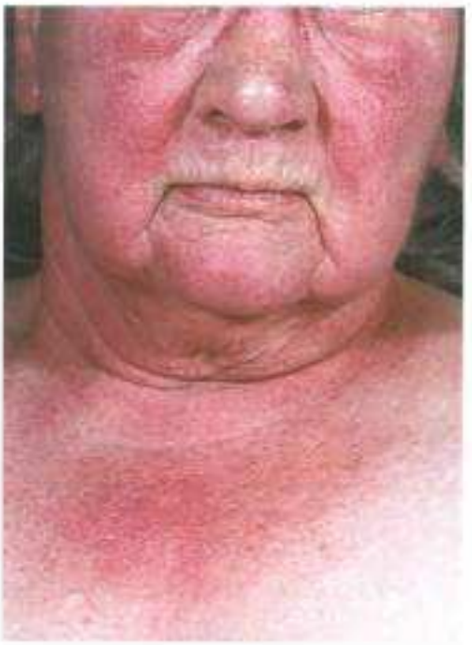


Fig. 21.33 Dermatomyositis. There is a distinctive mauve discoloration with oedema often in a light-exposed distribution.

affect the brain, which is rich in phospholipids, leading to transient ischaemic attacks, full-blown strokes, choreoathetosis, memory loss, stuttering speech and migraine. Myocardial infarction and valvular vegetations may occur. It is the second commonest cause of the Budd–Chiari syndrome from hepatoveno-occlusive disease. It is a major cause of acute Addison's disease. Smoking and the oral contraceptive pill are potentiating factors. It is sometimes called *Hughes's syndrome*.

Clinical Features

Symptoms

Recurrent miscarriages and thromboses are suggestive.

Morphology

There is livedo reticularis (Fig. 21.32), acrocyanosis, Raynaud's, digital ischaemia/gangrene, splinter haemorrhages and thrombophlebitis.

Distribution

The limbs and extremities.

Management

Skin biopsy should reveal a non-inflammatory thrombosis of small dermal blood vessels without vasculitis. The presence of the antibodies establishes the diagnosis. Anticoagulation is the treatment of choice for the thrombotic events associated with the primary and secondary forms of the syndrome. Sneddon's syndrome (generalized livedo reticularis associated with strokes and other thrombo-occlusive events) may be a related condition in that antiphospholipid antibodies are found in about half the patients.

Dermatomyositis

A rare set of autoimmune disorders that cause inflammation of striated muscle, leading to progressive proximal muscle weakness, associated with a specific cutaneous eruption and other organ involvement.

Aetiology

Dermatomyositis is four times less common than systemic LE. Onset is either juvenile or adult. There are various inflammatory forms: isolated polymyositis, isolated dermatomyositis, juvenile polymyositis/dermatomyositis, dermatomyositis associated with malignancy and polymyositis/dermatomyositis associated with antisynthetase antibodies (Jo1, PL7 and PL12), anti-Mi2, anti-Km, anti-Ro, anti-U1 RNP and especially PM-Scl antibodies (which occur in 25% of patients with PM/scleroderma overlap syndrome). HLA-DR3 is associated with the juvenile variety and a variety of histocompatibility antigens with the others. There are associations with other autoimmune diseases including Graves' disease. Environmental studies suggest an association with infection with *Toxoplasma gondii* and various viruses including Coxsackievirus. Similarities between polymyositis and inclusion body myositis suggest a viral aetiology; the demonstration of Jo-1 antibody in polymyositis further supports a viral aetiology, since the antigen for the Jo-1 antibody has similar characteristics to viral and muscle proteins. Malignancy is associated more closely with adult dermatomyositis than polymyositis, particularly ovarian cancer in females, lymphoma in males and carcinoma of the lung, breast, stomach and cervix. The incidence varies but is thought to be as high as 25%. In childhood, dermatomyositis is unrelated to malignant disease.

Clinical Features

Symptoms

Pruritus and fatigue are common. The affected muscles are sore and weak. The patient has difficulty combing the hair, climbing stairs, getting up from a chair and raising the neck when in bed, but distal muscle function is usually well preserved. Dysphagia may occur.

Morphology

There is a distinctive mauve erythema (Fig. 21.33), oedema and secondary poikiloderma (hyper- and hypopigmentation, epidermal atrophy and telangiectasia).

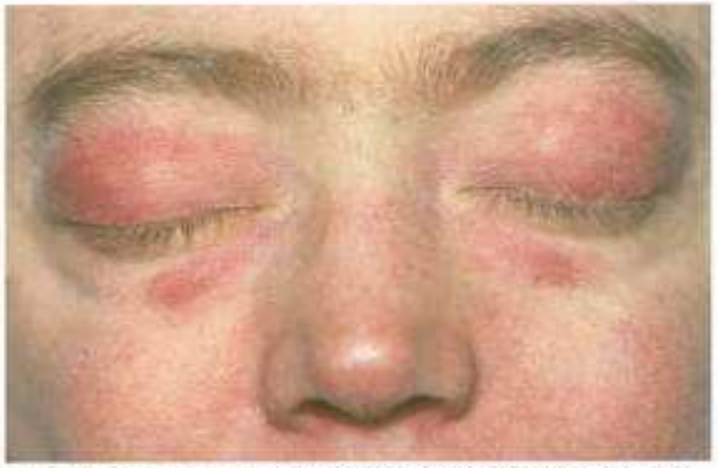


Fig. 21.34 Dermatomyositis. The heliotrope discoloration and oedema around the eyes are pathognomic. This woman is also cushingoid from systemic steroids. (Courtesy of Professor Lionel Fry, St Mary's Hospital.)

Fig. 21.35 Dermatomyositis. The mauve colour is not discernible in a black skin, but the oedema and pigmentation around the eyelids should give the clue to the diagnosis.

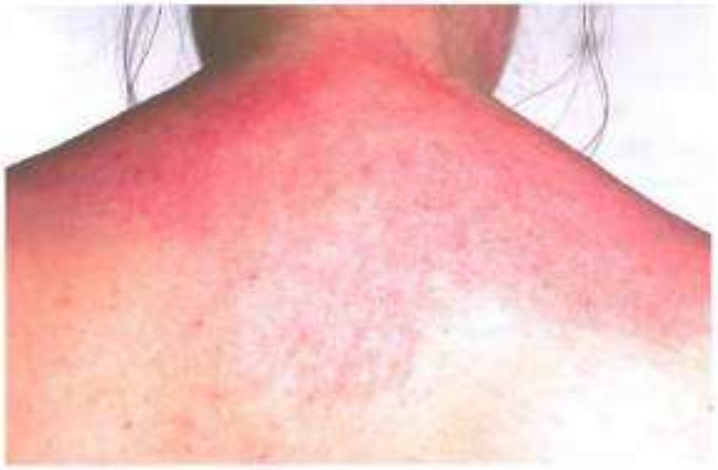


Fig. 21.36 Dermatomyositis. The mauve discoloration is striking. The upper back is often affected (so-called 'mantle sign').

Distribution

This is characteristic upper eyelids (Figs 21.34 and 21.35), forehead, cheeks, neck, upper back (Fig. 21.36) and extensor surfaces of the limbs (Fig 21.37), elbows, knees and ankles. The distinctive erythema over the knuckles, which may be papular (Figs 21.38, 21.39 and 21.40), is known as Gottron's sign. Cuticular splinter haemorrhages (Fig. 21.41), periungual erythema and erythema of the fingertips are helpful additional physical signs. The lesions may be followed by atrophy and pigmentation (poikiloderma).

The heliotrope colour (Fig. 21.42) and oedema of the upper eyelids, and the Gottron's papules, are specific for the disorder. The malar erythema, poikiloderma in a photosensitive distribution and the periungual and cuticular changes are not, for they may occur in LE. Recrudescence of the heliotrope eruption is proportional to disease activity, but not the Gottron's papules.

Acquired ichthyosis, cutaneous vasculitis, panniculitis, erythroderma and Degos-like lesions have all been described. Occasionally indurated plaques (Fig. 21.43) and papules secondary to mucin deposition may occur across the torso. The hands may be scaly, hyperkeratotic and pigmented and are known as mechanic's hands (Fig. 21.44).

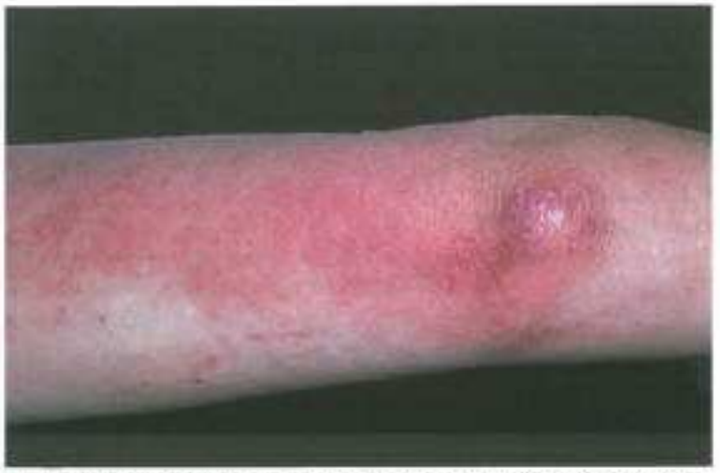


Fig. 21.37 Dermatomyositis. The arms and particularly the elbows are involved with a persistent erythema.

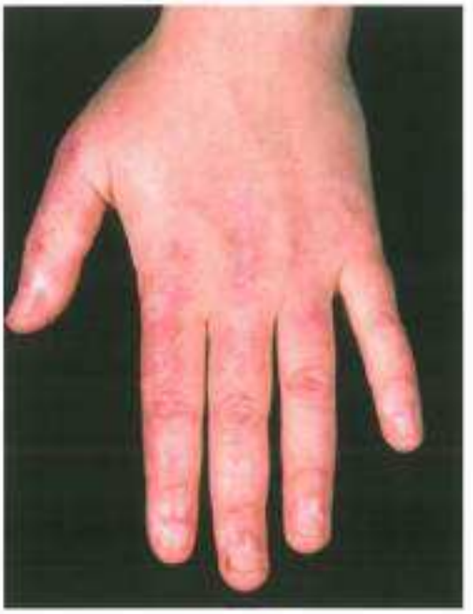


Fig. 21.38 Dermatomyositis. The mauve discoloration also occurs over the backs of the knuckles (same patient as Fig. 21.36). Her myopathy and skin eruption responded to a combination of systemic steroids, intravenous immunoglobulin and azathioprine.

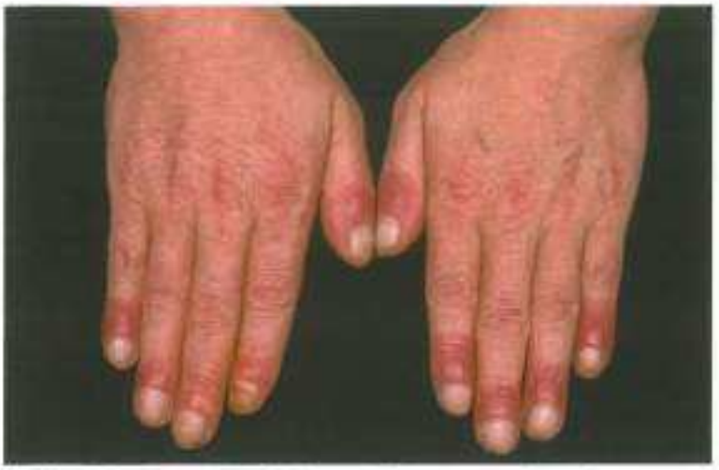


Fig. 21.39 Dermatomyositis. This man had the cutaneous signs of dermatomyositis without myositis. He was found to have human immunodeficiency virus infection.

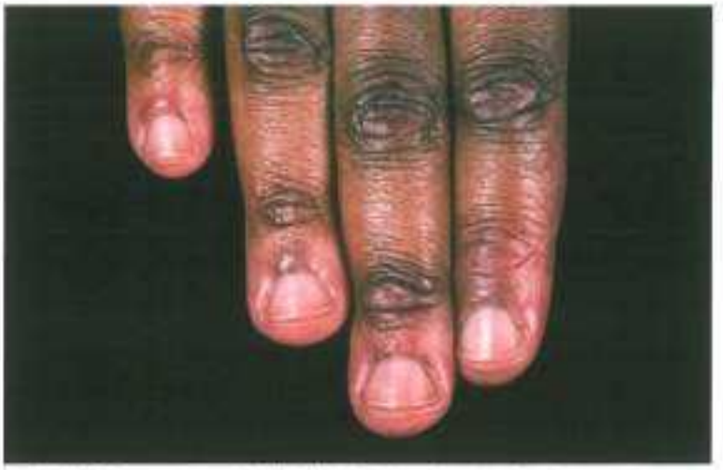


Fig. 21.40 Dermatomyositis. In black skin the pigmentation obscures the heliotrope discoloration, but the distribution of the eruption over the knuckles is enough to make the diagnosis.

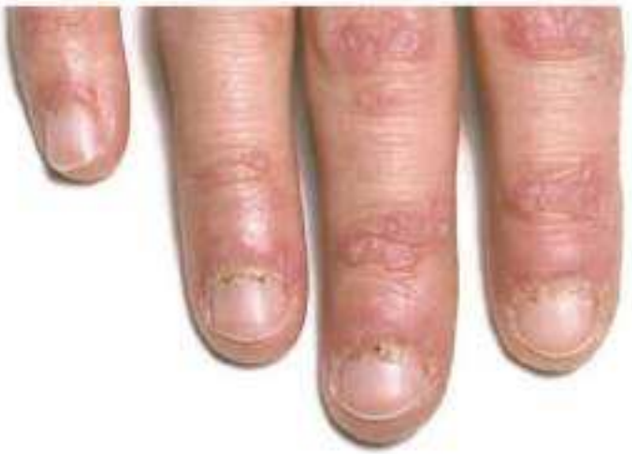


Fig. 21.41 Dermatomyositis. The mauve papules over the knuckles are known as Gottron's sign. Cuticular splinter haemorrhages are present.

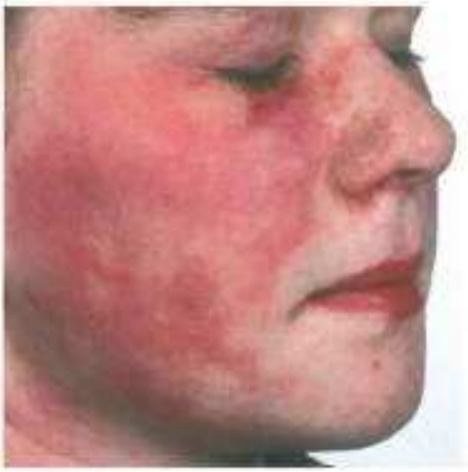


Fig. 21.42 Juvenile dermatomyositis. The eruption may spread onto the cheeks and may simulate systemic lupus erythematosus. Eyelid involvement is, however, characteristic.

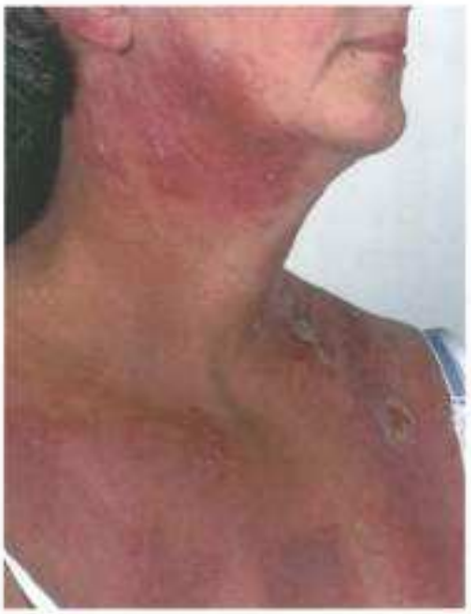


Fig. 21.43 Dermatomyositis. The mauve colour is distinctive. The neck and front of the chest are commonly involved and there may be poikilodermatous, sclerodermatous or mucinous plaques.

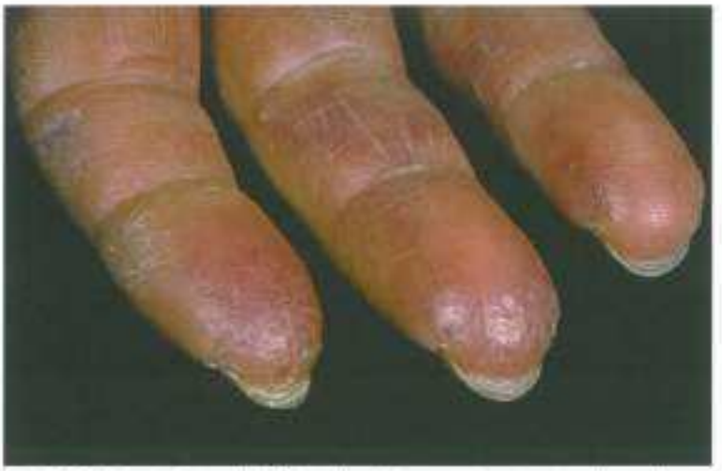


Fig. 21.44 Dermatomyositis. Fingertip erythema and scaling, sometimes known as mechanic's hands, may occur, in the antisynthetase antibody syndrome with fever, erosive arthritis, Raynaud's and interstitial lung disease.

Management and Course

The juvenile variety may spontaneously remit, especially if it is of acute onset. Alternatively, it may relapse and remit: the prognosis depends on the degree of muscle involvement and subsequent atrophy. Respiratory muscle or pharyngeal involvement may cause death through respiratory failure or aspiration of food or secretions. Widespread calcinosis (Figs 21.45, 21.46 and 21.47) may be present in involved muscles, particularly in children. Other abnormalities include hypertrichosis, lipoatrophy, symmetrical arthritis of large and small joints resulting in contractures, and malabsorption, infarction, ulceration, perforation and haemorrhage from gastrointestinal involvement. A diffuse interstitial pneumonitis may occur particularly in polymyositis, and antisynthetase antibodies are positive.

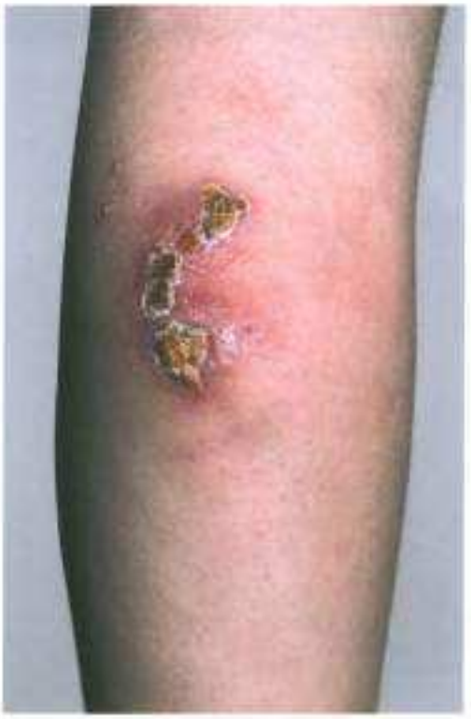


Fig. 21.45 Juvenile dermatomyositis. Calcinosis cutis is frequent in juvenile but not malignancy-associated dermatomyositis. The calcium deposits may extrude through the skin.

Dermatomyositis may occur without myositis in a small percentage and may remain so, or the patient may develop myositis some years later. Overlap syndromes predominantly occur in females. They present with polyarthritis, Raynaud's phenomenon, sclerodactyly and sicca syndrome and are more likely to have positive rheumatoid factors, ANAs, double-stranded DNA antibodies and Scl-70 antibodies or ENAs, usually RNP (ribonucleoprotein) but sometimes SSA and/or SSB.

In adults, the finding and successful treatment of an underlying malignancy can lead to cure. Occasionally, the malignancy may not be detectable until some years after the development of the disease. Risk factors are older age, atypical extensive severe cutaneous refractory disease and vasculitis, rapidly progressive myopathy (including diaphragmatic weakness and dysphagia), absence of interstitial lung disease and raised ESR. TIF-1-γ (P155/140) is positive in 85% of cancer-associated dermatomyositis. Lung cancer is commonest overall and ovarian in females. In patients where a malignancy is not found, management is the same as that for the juvenile type.

The diagnosis is clinical and is made from the skin changes and the progressive proximal symmetrical muscle weakness. There is no specific test. The diagnosis is established by muscle biopsy and electromyographic evidence of an inflammatory myopathy and raised muscle enzymes: aldolases, glutamic oxaloacetic transaminases, lactic dehydrogenases, aminotransferases and creatine phosphokinases. The ESR may or may not be raised. Non-myositis-specific antibodies are found. Low-titre ANAs are detected in the majority. An ANA titre greater than 1:160 is associated with a mixed connective tissue disorder. The pattern of nuclear fluorescence with labels for ANA is homogeneous or speckled rather than the rim fluorescence of LE. In the overlap syndromes, anti-RNP is associated with mixed connective tissue disease or systemic LE with myositis. Anti-Ku is associated with a myositis overlapping with scleroderma or systemic LE. Anti-PM-Scl is a unique subset with scleroderma limited to the face and hands, with Raynaud's phenomenon, dermatomyositis or polymyositis, non-deforming non-erosive arthritis with a positive rheumatoid factor and oesophageal and lung involvement. The Jo-1 antibody is more often positive in dermatomyositis with pulmonary complications. Myositis-specific antibodies directed against certain cytoplasmic proteins and RNA are found in approximately 30% of patients, particularly with those with disease not associated with a malignancy.

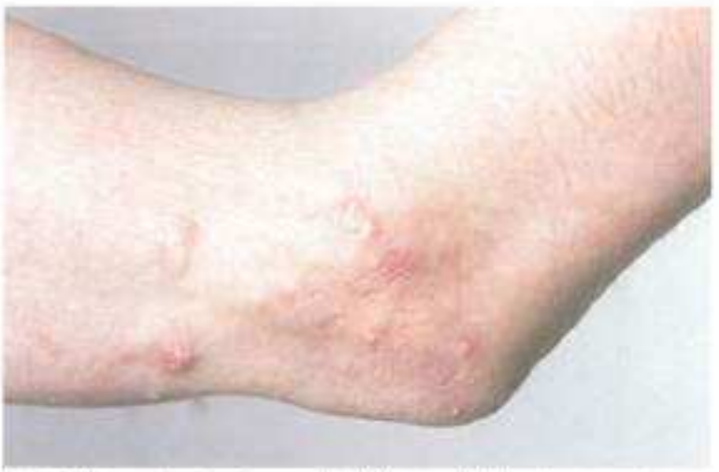


Fig. 21.46 Juvenile dermatomyositis. Widespread calcinosis may occur in juvenile disease. Hard yellow nodules are present.

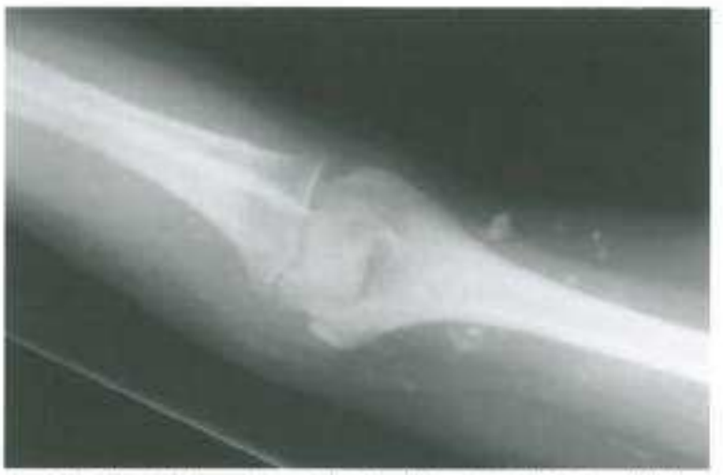


Fig. 21.47 Juvenile dermatomyositis. The calcinosis is visible in the affected muscles on radiographs. (Courtesy of St Mary's Hospital.)

Once malignancy has been excluded, complete remissions may be produced with judicious use of prednisolone starting at 40–60 mg daily. This is reduced by a quarter each month as muscle function returns (usually within 3 months) and the serum concentrations of muscle-specific enzymes are decreased. The prednisolone is maintained at 5–10 mg daily for 1 year. One in four patients do not respond to systemic steroids. Methotrexate, dosage 25–50 mg weekly, is a useful additional drug. Azathioprine (2 mg/kg per day) has a steroid-sparing effect and is frequently used in combination since the systemic steroids themselves may cause muscle atrophy. Hydroxychloroquine, plasmaphoresis, ciclosporin and pulse methylprednisolone, mycophenolate mofetil and rituximab are other therapies that have been employed. Calcinosis cutis may be surgically debrided under digital block. Rest is essential and physiotherapy is important to prevent contractures and wasting.

Scleroderma

Scleroderma is the prototype of fibrotic skin diseases, that is disorders characterized by excessive deposition of collagen and other connective tissue components leading to dermal fibrosis. Progressive systemic sclerosis affects not only the acral skin but also the heart, lung, kidney and gastrointestinal tract. A more benign subset of this disease is known as the CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia). Scleroderma may be limited to the skin (morphoea) in a plaque, linear or generalized form. Scleroderma-like changes occur in mixed connective tissue disease or may overlap with LE and dermatomyositis.

Eosinophilic fasciitis is a thickening and induration of the skin associated with eosinophilia and an inflammatory infiltrate, especially of eosinophils, in the subcutaneous fascia and muscles. A similar condition has occurred in patients who have ingested L-tryptophan.

Dermal fibrosis may occur in certain metabolic and immunological diseases and in particular in chronic graft-versus-host disease, porphyria, phenylketonuria, carcinoid syndrome and some paraproteinaemias. There is also a syndrome of digital sclerosis and joint contractures that occurs in poorly controlled juvenile diabetics. Finally, dermal fibrosis may be induced chemically. Bleomycin and pentazocine may produce a scleroderma-like eruption, as can long-term exposure to silica dust. A scleroderma-like condition with systemic involvement that includes angiosarcoma of the liver has also been described in workers exposed to vinyl chloride, particularly those who clean reactors. A *nephrogenic systemic fibrosis* occurs after exposure to gadolinium-based contrast media. It causes scleroderma of the lower legs and contractures. It may also cause wrinkled redundant skin simulating cutis laxa. It may respond to rapamycin.

SYSTEMIC SCLEROSIS

An autoimmune disorder of unknown aetiology that causes scleroderma, Raynaud's phenomenon and fibrosis of the gut, heart, lungs and kidneys.

Aetiology

It is an autoimmune disorder with abnormal deposition of collagen and an obliterative vasculopathy affecting the skin, kidneys, lung, heart and gastrointestinal tract. There is increased synthesis and decreased degradation of extramatrix components, mainly type I and III collagen. Inflammatory cells infiltrate sclerodermatous lesions early in the disease. Profibrotic cytokines and growth factors are produced, which activate fibroblasts and produce large amounts of collagen. It is associated with Sjögren's syndrome and Hashimoto's thyroiditis. There may be hypergammaglobulinaemia, a positive rheumatoid factor and a speckled or nuclear pattern of fluorescent ANA, which are not related to the severity of the disease. Antinucleolar antibodies and antibodies to uracil base pairs of RNA and to collagen types I and IV, particularly in those with diffuse interstitial lung disease, may be present. Anticentromere antibodies are positive in 80% of patients with limited systemic sclerosis and antitopoisomerase I (anti- Scl70) antibodies are positive in a third of patients with diffuse systemic sclerosis.

Clinical Features

Symptoms

It usually presents with Raynaud's phenomenon (Fig. 21.48). On exposure to cold, the fingers go white as a result of intense arteriolar vasoconstriction, then blue from cyanosis and lastly red, warm and painful following reactive vasodilatation. Variable deformity and dysfunction of the fingers result (Fig. 21.49). Some patients have pain and stiffness of the joints.

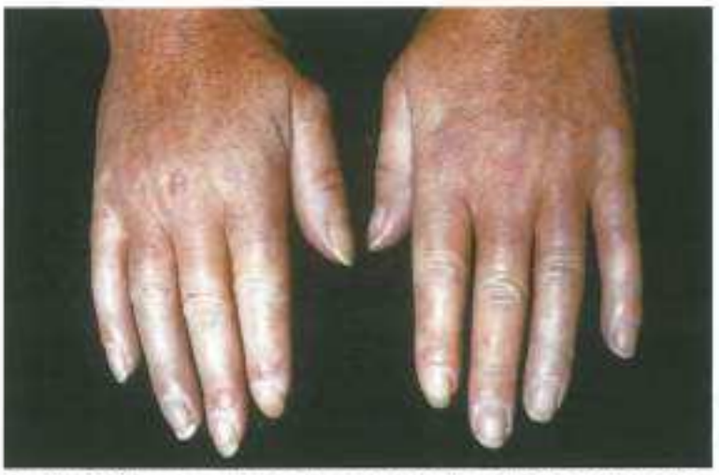


Fig. 21.48 Scleroderma. It frequently presents as Raynaud's phenomenon. The skin goes white in response to cold. Ultimately sclerodactyly results, with tapering of the fingers. (Courtesy of St Mary's Hospital.)

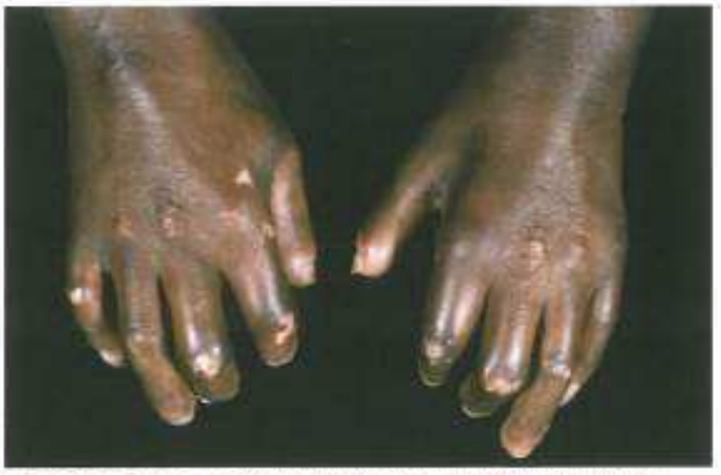


Fig. 21.49 Scleroderma. The skin is tethered and hardened. Deformity has resulted. Fingertip vessel occlusion leads to ulceration, gangrene and loss of the digits.

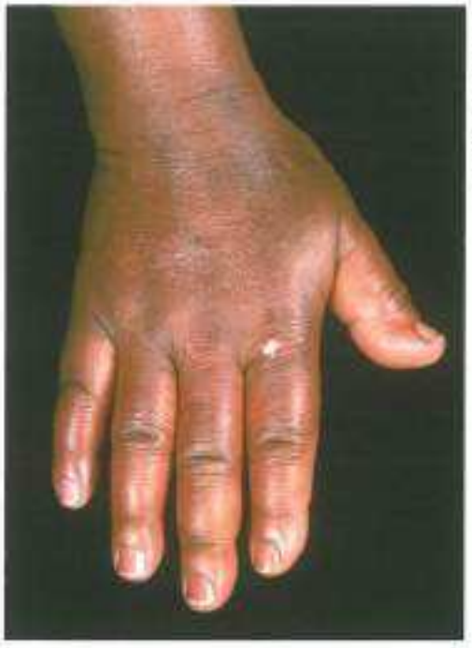


Fig. 21.50 Scleroderma. There is chronic non-pitting oedema of the fingers giving rise to a sausage-shaped appearance. Note the macule of vitiligo.

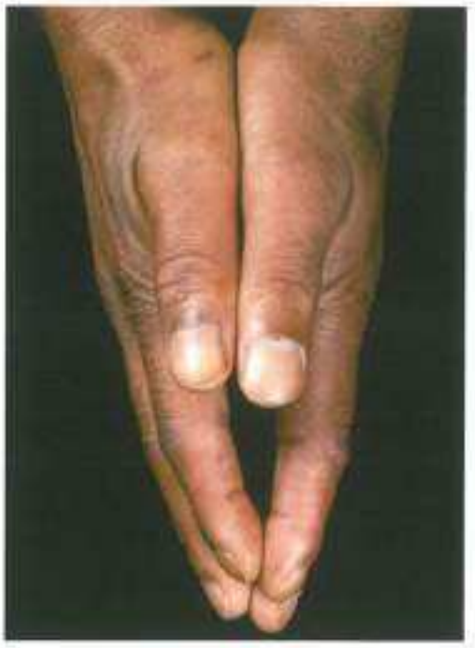


Fig. 21.51 Scleroderma. Acrosclerosis results and the patient is unable to extend the fingers fully (the 'prayer sign').

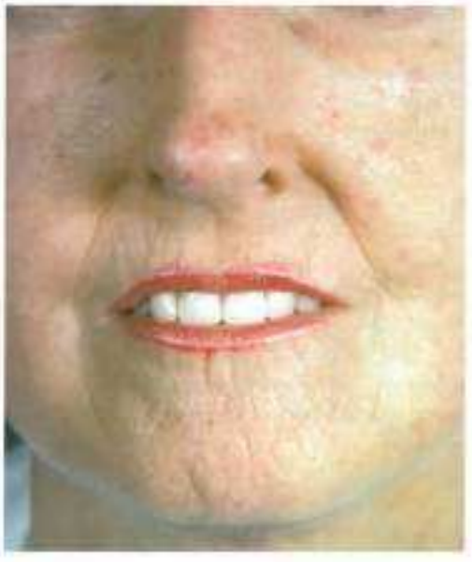


Fig. 21.52 Scleroderma. Furrows radiate from the mouth, which becomes shrunken. Matt-like telangiectasia may occur in the CREST syndrome. (Courtesy of St Mary's Hospital.)

Morphology and Distribution

There may be a chronic non-pitting oedema of the fingers (Fig. 21.50). Subsequent structural changes result in acrosclerosis (Fig. 21.51). The skin becomes tethered and has a hardened (sclerotic) feel. There is loss of the normal skin creases. It is not possible to pinch the skin and there is tapering of the fingers and thumbs caused by atrophy of the pulp of the tips. Digital ischaemia leads to cutaneous infarction and ulceration and possibly gangrene of the fingertips.

The skin of the face is also involved. There is loss of subcutaneous tissue and the nose has a beak-like appearance. The oral aperture becomes smaller (Fig. 21.52) and there is difficulty in opening it to its full extent. Furrows radiating out from the mouth are typical.

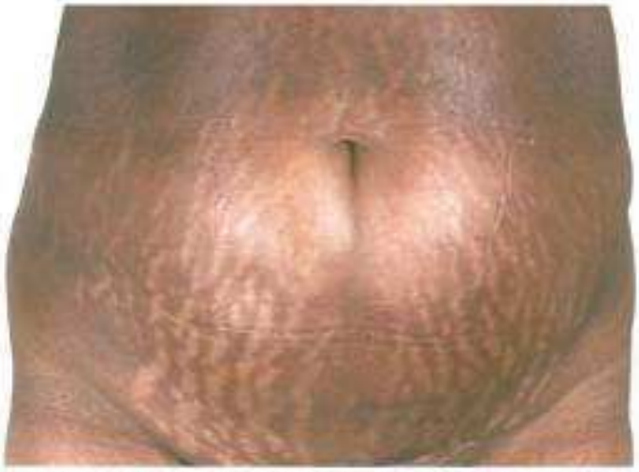


Fig. 21.53 Scleroderma. This Afro-Caribbean woman presented because she had noticed that her skin had become generally darker. The hands (Fig. 21.49) were then noted by the physician to be sclerodermatous.

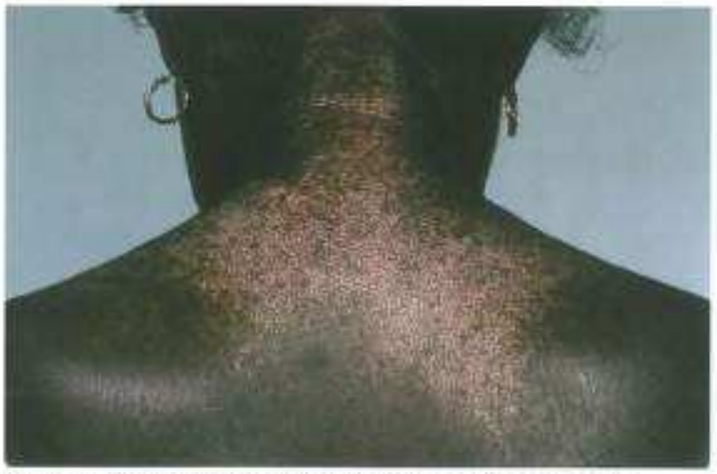


Fig. 21.54 Scleroderma. Stippled vitiligo quite commonly accompanies scleroderma. Both are auto-immune disorders.

Additional features are matt-like telangiectasia on the face and calcinosis, particularly in the fingers but also in the soft tissue elsewhere. Hirsutism and hyperpigmentation (Fig. 21.53) (Addisonian type) regularly accompany the disease. Vitiligo may occur (Fig. 21.54).

There are four types:

1. A rapid cutaneous sclerotic progression (*diffuse cutaneous systemic sclerosis*) from distal to truncal scleroderma with few telangiectases and internal organ involvement (pulmonary fibrosis, renal failure, gastrointestinal and myocardial disease). Anti-Scl-70 and antitopoisomerase I antibodies are positive. Anticentromere antibodies are usually negative. The prognosis is poor.
2. Limited systemic sclerosis, characterized by calcification, Raynaud's phenomenon, oesophageal involvement, sclerodactyly and telangiectasia (*CREST syndrome*). It has a more favourable prognosis. Visceral involvement is limited. Vascular lesions occur on the face, upper trunk, hands, nailfolds, lips, oral mucous membranes and throughout the gastrointestinal tract (gastrointestinal bleeding occasionally occurs). The condition is characterized by the finding of antibodies to centromeric chromatin.
3. A rare diffuse sclerosis with disseminated telangiectasia and antifibrillary antibodies.
4. Patients with combined features of scleroderma, LE and dermatomyositis are grouped together under the title of *mixed connective tissue disease*. Many have a specific antibody to an ENA as well as a positive speckled ANA. Raynaud's phenomenon and myositis are common, but skin lesions other than hair loss are less so. The condition is said to be less aggressive than most connective tissue disorders because the kidneys are infrequently involved and the condition responds well to systemic steroids. Scleroderma may also be associated with primary biliary cirrhosis.

Management and Course

The prognosis is determined by the degree of systemic organ involvement. Pulmonary disease may result in terminal fibrosis. Pericarditis, effusions, conduction defects, arrhythmias and heart failure are fairly common cardiac complications. Renal failure and hypertension may occur. In the gastrointestinal tract, loss of peristalsis leads to difficulty in swallowing and there may be malabsorption through involvement of the small bowel. Diverticula may occur in the large gut.

The diagnosis is a clinical one. The AMA criteria include diffuse proximal sclerosis, sclerodactyly, bibasilar pulmonary fibrosis, Raynaud's phenomenon, abnormal nailfold capillaries and positive ANA. Other autoantibodies may be positive and oesophagitis, digital ulceration, telangiectases and calcinosis are suggestive features. Histologically, there is extensive collagenization of the dermis with loss of the appendage structures (Fig. 21.55). In early lesions, a perivascular chronic inflammatory cell infiltrate is present at the interface between the dermis and subcutaneous fat. In late lesions, fibrointimal proliferation is common and occlusion may result in gangrene.

Treatment is unsatisfactory. However, better control of hypertension with ACE inhibitors and pulmonary interstitial disease with immunosuppressants and proton pump inhibitors for oesophageal disease have helped to prolong life. Systemic steroids, azathioprine, methotrexate, chlorambucil, and interferon-γ have been used for their immunomodulatory effects. Prostaglandins (injected inter-arterially) and vasodilators (calcium channel, such as nifedipine) are employed for their effects on Raynaud's phenomenon and PUVA, UVA 1 and penicillamine for their effects on the skin. UVA 1 (340–400 nm) reaches the subcutis (as opposed to UVB, which reaches only the papillary dermis) and is used in low-, medium- or high-dose emissions. It is best for morphoea, but scleroderma and sclerodermatous graft-versus-host disease may improve.

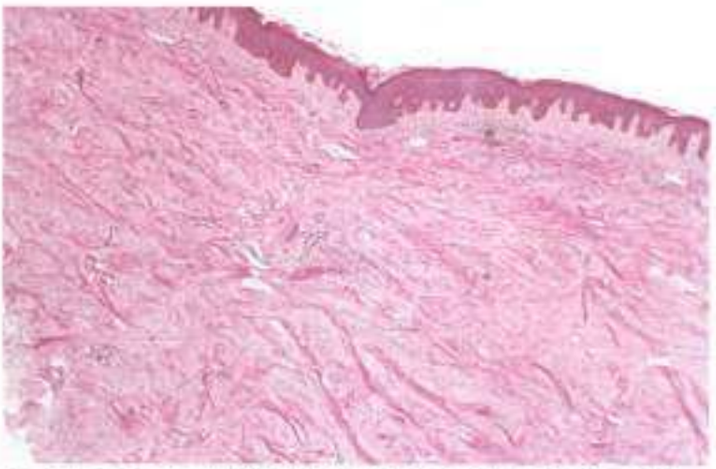


Fig. 21.55 Scleroderma. The reticular dermis is expanded by densely packed, broad bundles of relatively acellular collagen. Cutaneous appendages are markedly reduced in number and an atrophic hair follicle is seen (mid picture). Eccrine sweat ducts are entrapped and compressed by the dense fibrous tissue.

D-Penicillamine is a potent inhibitor of collagen cross-links because it complexes with lysine- and hydrolysine-derived aldehyde groups required for synthesis of stable collagen cross-links. It causes thinning of the skin when used to treat Wilson's disease. It is possibly most useful for acute rapidly progressive disease. Bone marrow transplantation has produced mixed results.

EOSINOPHILIC FASCIITIS

A sclerodermatous process of the extremities that spares the hands and feet, associated with arthralgia, eosinophilia, hypergammaglobulinaemia and fasciitis with or without myositis.

Aetiology

The cause of eosinophilic fasciitis (also known as *Shulman's syndrome*) is unknown and it is a moot point whether it is a distinct entity or a variant of scleroderma. It is characterized by an eosinophilia and hypergammaglobulinaemia. A minority have positive ANA or anti-DNA antibodies. Histologically, there is a round cell infiltration of the fascia and muscles, with plasma cells, lymphocytes and sometimes eosinophils. The condition often begins after undue physical exertion and seems to be more common in the autumn. It is most common in older males. There is no associated Raynaud's phenomenon or visceral involvement, unlike in scleroderma.

A similar syndrome associated with muscle dysfunction and raised muscle enzymes occurs in patients who have ingested L-tryptophan (*the eosinophilia myalgia syndrome*); the reason is unknown but there may be an abnormality in tryptophan metabolism in scleroderma, and dermal fibrosis does occur in the carcinoid syndrome, where 5-hydroxytryptamine, a component of tryptophan metabolism, is abnormal.

Clinical Features

Symptoms

Pain and swelling often following undue physical exertion. Limitation of movement.

Morphology

The skin is firm and tightly bound down in a sclerodermatous fashion.

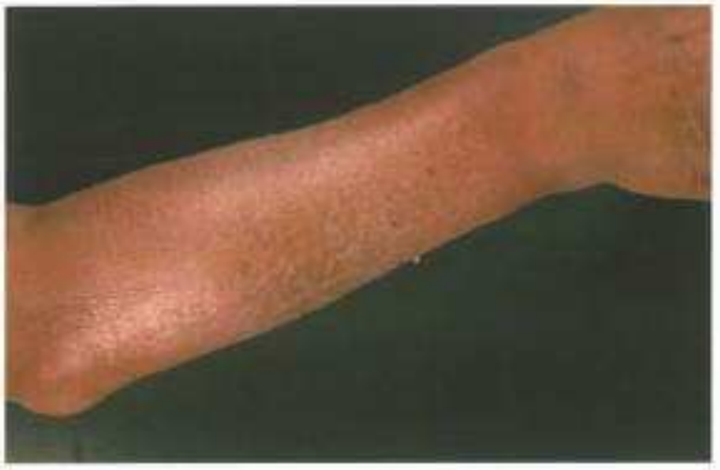


Fig. 21.56 Eosinophilic fasciitis. The skin of the forearms is shiny, bound down and sclerotic, but the hands are unaffected. The swelling is painful.

Fig. 21.57 Scleredema of Buschke. The skin has a wooden indurated papular consistency.

Distribution
The extremities (Fig. 21.56), but sparing the feet and hands.

Systemic features
There may be arthralgia, peripheral neuropathy, cytopenias and eosinophilia, and joint contractures.

Management
A deep surgical biopsy of the fascia and muscle is helpful for a pathological diagnosis. Systemic steroids, dapsone and other immunosuppressants may be beneficial. The condition may resolve spontaneously.

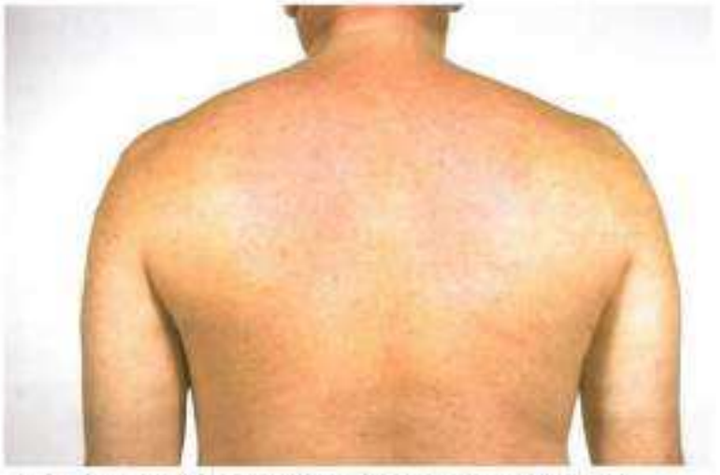


Fig. 21.58 Scleredema of Buschke. It begins acutely often across the shoulders following an infection or associated with complicated diabetes mellitus or a monoclonal gammopathy.

Scleredema of Buschke

An induration of the skin particularly of the upper back, which may occur suddenly after a prodrome or with complicated diabetes.

Aetiology
The cause is unknown. There is replacement of the subcutaneous tissue by a fibromucinous connective tissue. There are four types. One is preceded by a viral or streptococcal illness, and recovery within a few months occurs. The second is associated with severe maturity-onset diabetes mellitus. The patients are usually obese, resistant to therapy and have cardiovascular disease and diabetic retinopathy. The third is associated with a monoclonal gammopathy and the fourth has no positive associations.

Clinical Features
Symptoms
The patient may have a low-grade fever, malaise, myalgia and arthralgia, which are followed very suddenly by non-pitting induration of the skin.

Morphology
The skin has a wooden-like consistency (Fig. 21.57) that is diffuse with loss of markings; and rather shiny sometimes preceded by a transitory erythema.

Distribution
Particularly across the shoulders (Fig. 21.58) and around the neck. It may spread to the face, where there is a lack of expression, to the arms and chest and, occasionally, to the buttocks, legs and abdomen.

Management
The diagnosis is clinical. The antistreptolysin titre may be raised if the preceding prodrome is streptococcal. The histology shows thickened collagen bundles in the reticular dermis separated by mucin, increased numbers of fibroblasts and dermal oedema. An Alcian blue stain may reveal excess hyaluronic acid. There is no specific treatment, although some respond to electron beam therapy.

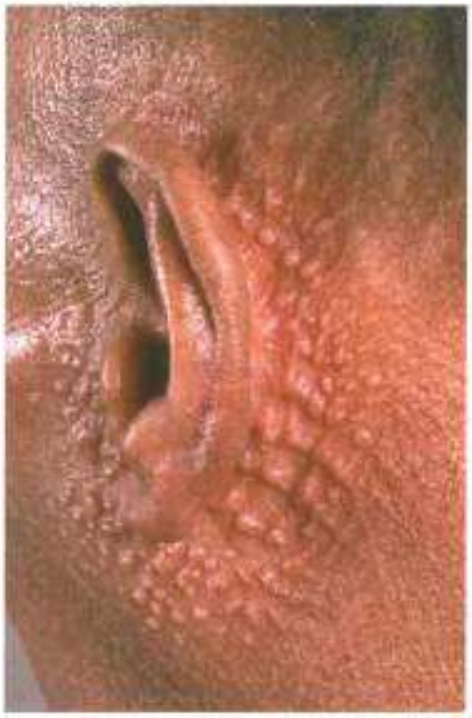


Fig. 21.59 Lichen myxoedematosus. Small, dome-shaped, lichenoid papules arranged in a linear manner are characteristic. The backs of the ears are usually involved.

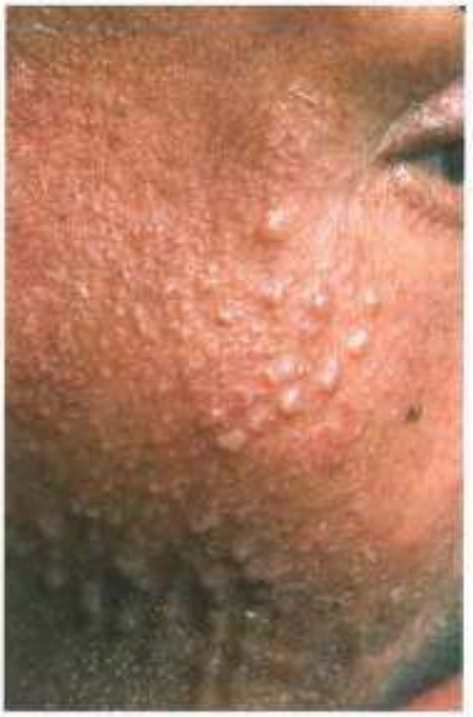


Fig. 21.60 Lichen myxoedematosus. Discrete dome-shaped flesh-coloured papules (papular mucinosis) are characteristic. This patient had an IgA paraproteinaemia.

Lichen myxoedematosus

A disorder of unknown aetiology associated with a characteristic lichenoid and a sclerodermoid eruption on the face and hands, mucin deposition and a paraproteinaemia.

Aetiology

There are two variants – localized papular and limited to the arms, legs and trunk without sclerotic features or paraproteinaemia, and systemic with extensive papules becoming sclerodermoid with skin thickening, sclerodactyly and limited oral and joint mobility. A monoclonal gammopathy (and infrequently multiple myeloma) is usually present. It is of an IgG class with predominantly λ light chains, although IgA and IgM paraproteins may occur.

Other haematological malignancies including leukaemia have been described, which may be secondary to treatment. Deposits of the immunoglobulins may be found in the dermis. Serum from these patients does stimulate fibroblast proliferation so there may be a circulating factor that is as yet unidentified. The disorder affects both sexes and occurs in middle years. It is rare.

Clinical Features

Symptoms

It may be itchy.

Morphology

Small, dome-shaped, flesh- to cream-coloured, firm, waxy, lichenoid papules (also known as *papular mucinosis*) arranged in a linear manner (Fig. 21.59) make a distinct clinical appearance.

Distribution

They occur on sun-exposed areas (Fig. 21.60), particularly the face (especially the glabella with marked vertical creasing and behind the ears) and backs of the hands but may be extensive, with widespread sclerosis (often known as *scleromyxoedema*).

Systemic features

There may be gastrointestinal dysmobility and malabsorption, encephalopathy and seizures, rheumatic and pulmonary involvement.

Diagnosis and Management

The diagnosis is made by a combination of the striking clinical appearance associated with the demonstration of mucin and glycosaminoglycan in the dermis and the presence of a paraproteinaemia. There is no satisfactory therapy, although patients have been reported as benefiting from courses of melphalan, cyclophosphamide, electron beam therapy, IVIG, thalidomide and lenalidomide. Autologous peripheral blood stem cell transplantation may give a durable but not permanent remission.

Morphoea

A localized sclerosis of the skin, possibly of an autoimmune nature.

Aetiology

The cause is unknown, but there is fibroblast proliferation and excess accumulation of extra-cellular matrix proteins, especially collagen. The histology, histochemistry and electron microscopy are identical to those of systemic sclerosis but morphoea is localized to the skin and has no systemic consequences. The condition is sometimes precipitated by trauma, including X-ray therapy, and cases have been reported secondary to penicillamine therapy. Experimentally, it has been shown that normal skin grafted into a plaque of morphoea assumes the characteristics of morphoea. There is an increase in concomitant and familial autoimmune disease, especially in disseminated morphoea, e.g. SLE, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, thryoiditis and myasthenia gravis. *Borrelia burgdorferi* is possibly associated with a severe aggressive variety in childhood with high ANA titre.

Clinical Features

Symptoms

Patients describe a firm patch.

Morphology and distribution

- **Localized morphoea** A single oval or round plaque with a smooth shiny surface. The skin is tethered, as in scleroderma. There is loss of hair in the area and the margin is initially a lilac colour (Fig. 21.61), although it subsequently becomes brown (Fig. 21.62) as it disappears. After a number of years it may resolve spontaneously. The plaque can occur anywhere, but particularly thighs, abdomen and breast (Fig. 21.63).
- **Generalized morphoea** Rarely, extensive involvement occurs (Fig. 21.64), sometimes with muscle atrophy without any systemic acral disease (unlike scleroderma).
- **Linear morphoea** Linear forms occur, especially in children. These may be disfiguring or result in limited mobility and contracture since both superficial and deeper layers of the dermis are involved. The limbs, head and trunk are the common sites affected. On the face, the deformity left by the loss of subcutaneous tissue has been likened to a *coup de sabre* (Fig. 21.65). It may be related to the Parry–Romberg syndrome of epilepsy, eye signs (keratitis, cataracts, ptosis, enophthalmos and recalcitrant anterior uveitis) and hemifacial atrophy.
- **Atrophic morphoea** This is an atrophic variant that occurs in a zosteriform manner and is known as *zosteriform atrophoderma of Pasini and Pierini* (Fig. 21.66). The lesions may be single or multiple, slightly depressed and bluish or brown in colour. Deeper atrophy may occur, particularly on the back or paraspinal area (*Morphoea profunda*) (Fig. 21.67).

Management

Histologically, there is a slight atrophy of the epidermis with loss of the dermal appendages and degeneration of dermal collagen. The localized variety may resolve spontaneously or with superpotent glucocorticosteroids, or intralesional triamcinolone. Plastic surgery and dermal fillers may benefit the coup de sabre type. For generalized morphoea, penicillamine, high-dose ultraviolet A irradiation (340–400 nm) and PUVA, extracorporeal photophoresis, pulse high-dose intravenous steroids and methotrexate have been tried.

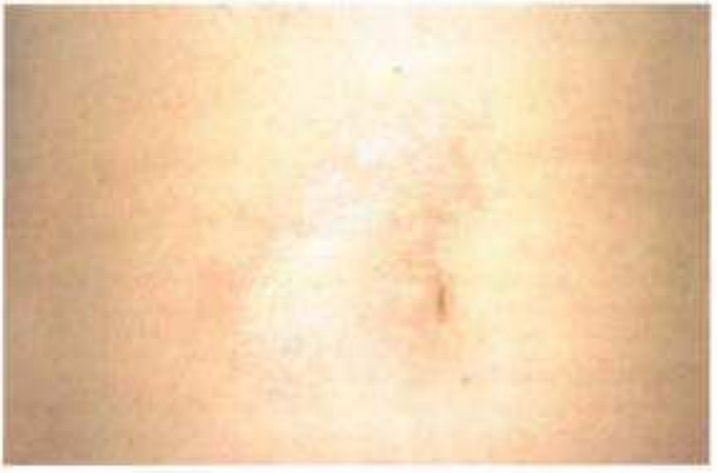


Fig. 21.61 Morphoea. The plaque has a shiny, smooth surface. It is tethered. A lilac margin is characteristic.

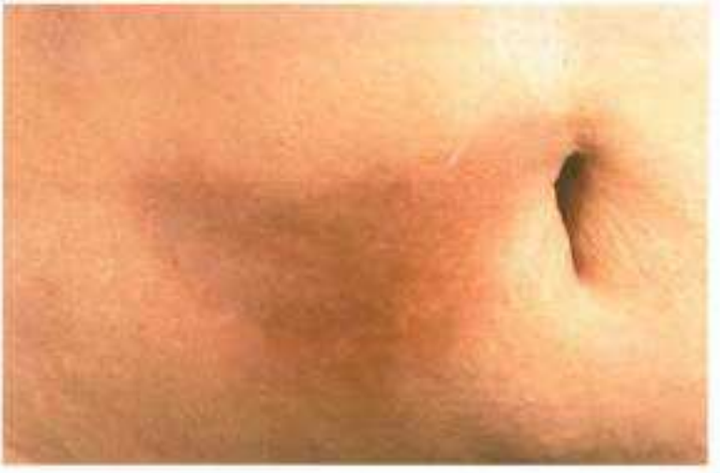


Fig. 21.62 Morphoea. As the condition recovers, a brown discoloration occurs. The abdomen is a common site.

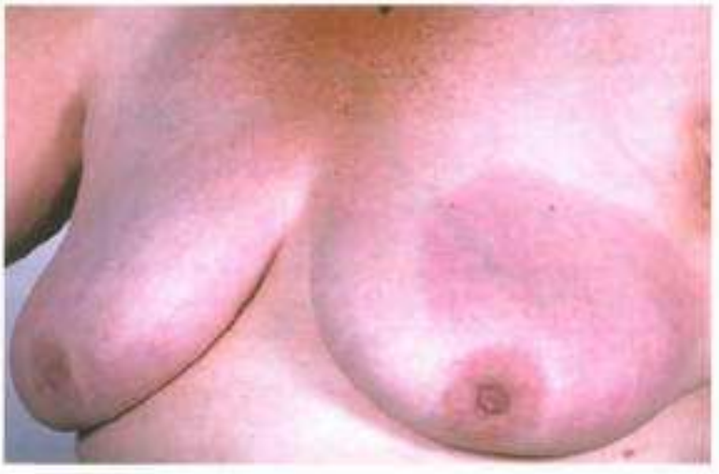


Fig. 21.63 Morphoea. The breast is a common site. The lesion is usually solitary, indurated and mauve, becoming pigmented. Superpotent topical steroids are helpful.

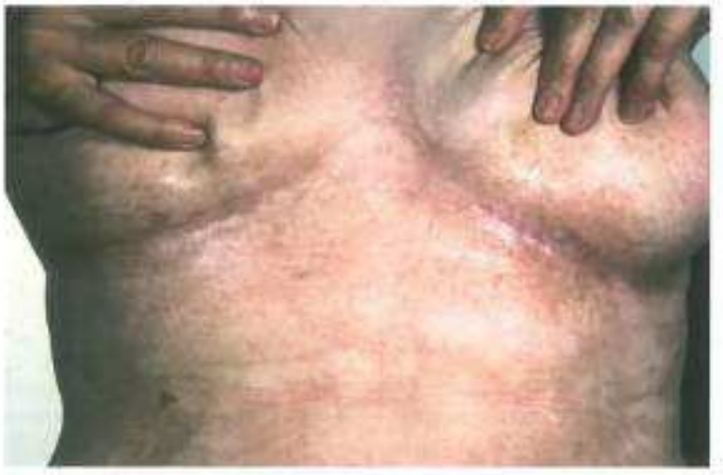


Fig. 21.64 Generalized morphoea. Widespread sclerodermatous plaques occur. UVA 1 phototherapy is increasingly used.

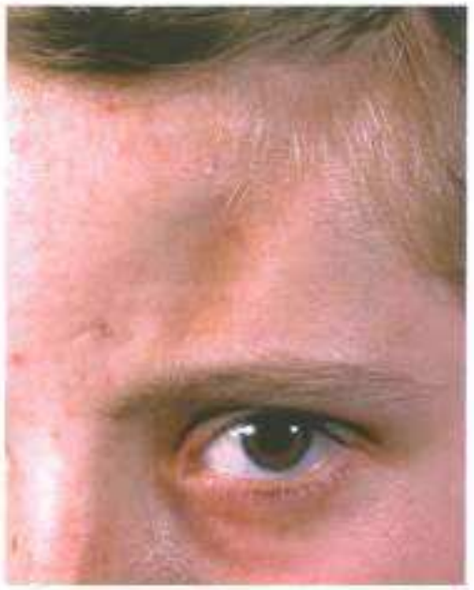


Fig. 21.65 Linear morphoea. The linear sclerotic depression has been likened to a blow from a sabre. Seizures may occur.

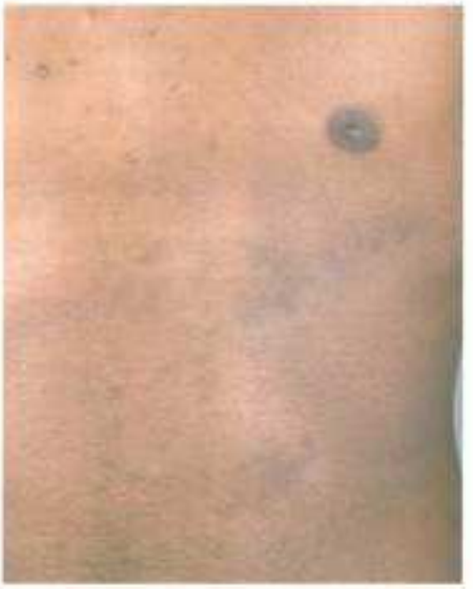


Fig. 21.66 Zosteriform atrophoderma. Single or multiple slightly depressed bluish or brown lesions occur in a zosteriform distribution.

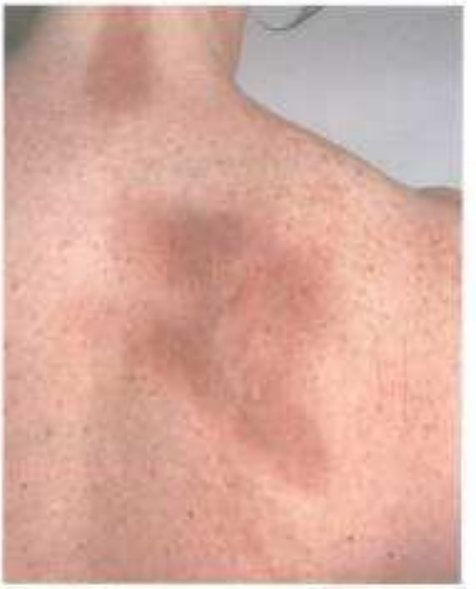


Fig. 21.67 Morphoea profunda. One or several deep atrophic areas occur particularly adjacent to the spine.

Lichen sclerosus et atrophicus

An autoimmune disorder that results in white, sclerodermatous papules or plaques of the skin, particularly of the genitalia.

Aetiology

It occurs at any age, but in women it is bimodal, prepubertal (including infancy, when it may involute) and postmenopausal. Ten per cent of the genital cases occur in children. It affects all races but is reported most in Caucasians, particularly females. The isomorphic phenomenon is described. Organ-specific autoantibodies are often present, particularly those associated with thyroid disease and diabetes mellitus. There is a slightly increased association with HLA-B40. It is probably a separate condition from morphoea. Circulating basement membrane antibodies and immunoreactants against extracellular matrix protein 1 are found in lichen sclerosus but not in morphoea.

Clinical Features

Symptoms

Genitalia

- **Females** It may be extremely pruritic or cause burning.
- **Males** It may be difficult to retract the foreskin or to micturate.

Morphology and distribution

Genital lesions

- **Females** Shiny, white and smooth-surfaced papules, which coalesce, occur in a symmetrical and well-defined manner around the vulva and the anus (Fig. 21.68) and sometimes onto the inner aspect of the thighs. They become atrophic (Fig. 21.69) with small telangiectases and purpura. Shrinkage of the vulval tissue results in obliteration of the labia majora and minora and introitus. Squamous cell carcinomas occasionally supervene.

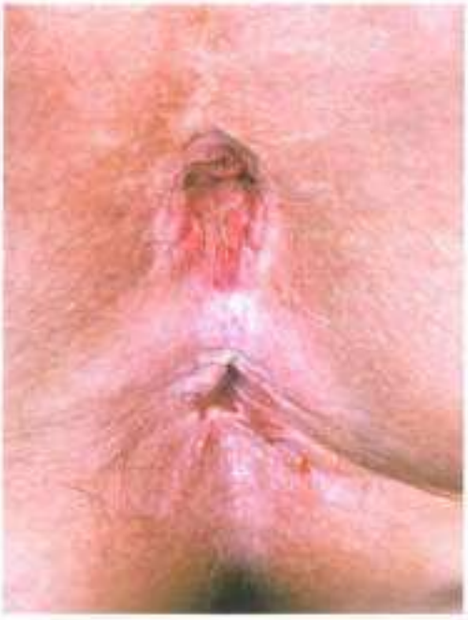


Fig. 21.68 Lichen sclerosus et atrophicus. Symmetrical, shiny, ivory-white papules coalesce around the vulva and anus causing obliteration of the normal architecture of the vulva. There is an 8% risk of malignant transformation.

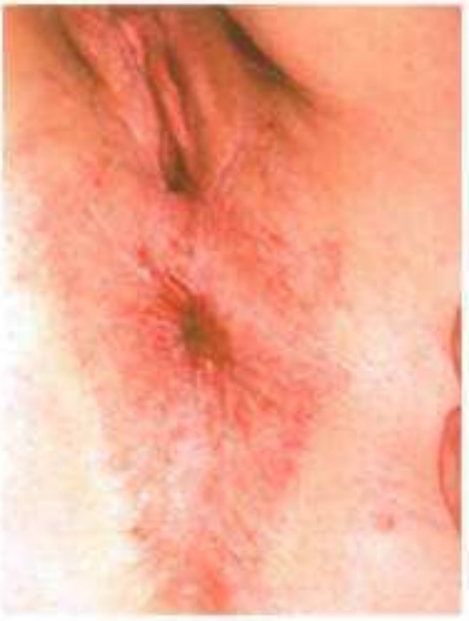


Fig. 21.69 Lichen sclerosus et atrophicus. Wrinkling (atrophy) of the skin is present in addition to the white papules around the anus. The condition is very pruritic but responds to superpotent steroids.

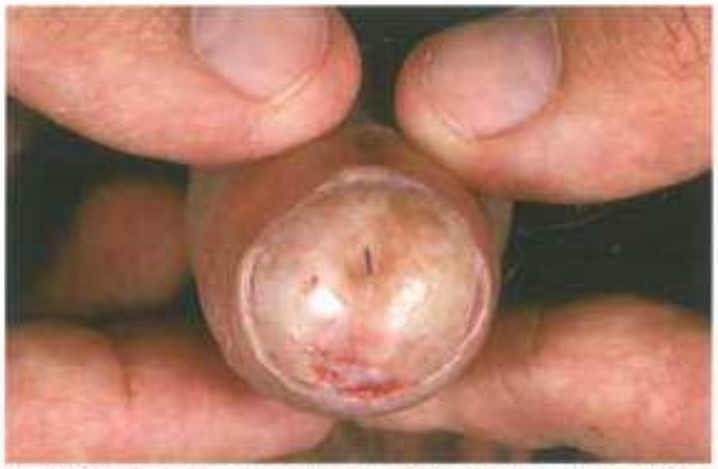


Fig. 21.70 Lichen sclerosus et atrophicus. White sclerotic papules are visible on the glans. Haemorrhage occurs readily into the atrophic area. Note the meatal stenosis.

- **Males** Ivory-white papules, atrophy, telangiectasia and purpura occur on the foreskin and glans penis (Figs 21.70 and 21.71). The condition is sometimes known as *balanitis xerotica obliterans*. Squamous cell carcinoma occurs very rarely. In boys, lichen sclerosus et atrophicus is a common and distinctive cause of phimosis and requires circumcision.

Extramucosal changes

These are more common in females. They consist of ivory-white, lichenoid papules that become atrophic (Fig. 21.72) and coalesce into plaques (Fig. 21.73) occurring, usually symmetrically, on the fronts of the wrists (Fig. 21.74), neck, upper back, shoulders and around the umbilicus. Haemorrhage may occur into the atrophic areas (Fig. 21.75). They may be extensive (Fig. 21.76) and may occur in the absence of genital lesions.

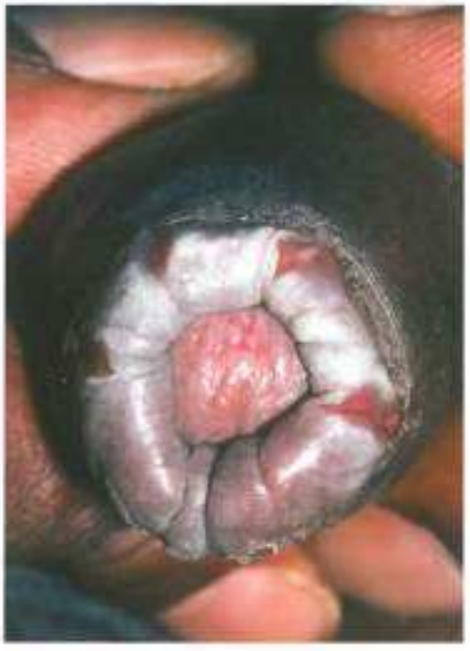


Fig. 21.71 Lichen sclerosus et atrophicus. Ivory-white papules with telangiectasia are present. The foreskin has become tethered and fissured. Retraction is restricted. Superpotent steroids are beneficial.

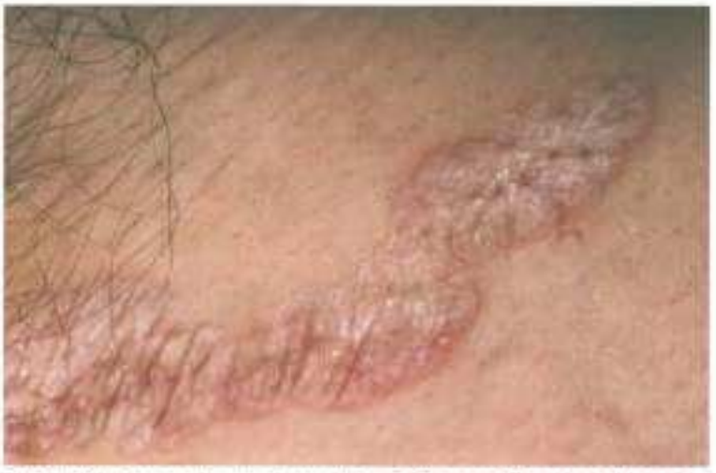


Fig. 21.72 Lichen sclerosus et atrophicus. The ivory-white papules become atrophic and the skin is thin and wrinkled. A brown discoloration occurs as it resolves.

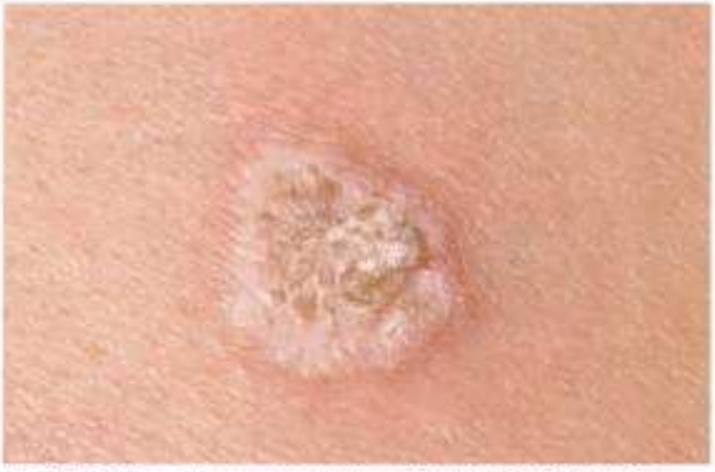


Fig. 21.73 Lichen sclerosus et atrophicus. The white, lichenoid papules coalesce into plaques. Note the lilac-coloured margin.

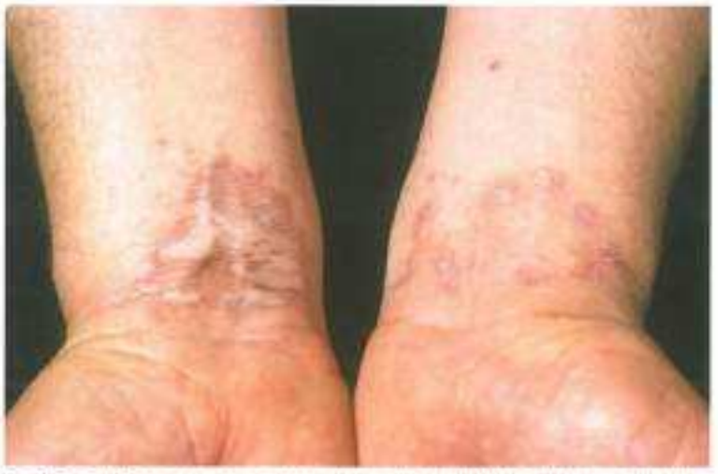


Fig. 21.74 Lichen sclerosus et atrophicus. Ivory-white papules surrounded by a lilac discoloration occur symmetrically, especially on the wrists. (Courtesy of St Mary's Hospital.)

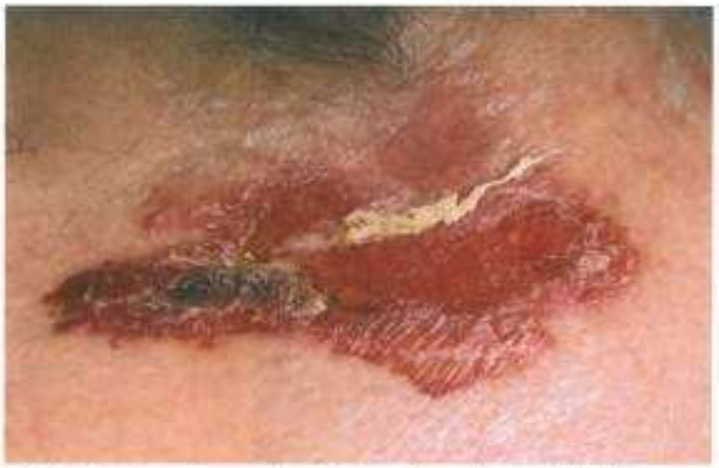


Fig. 21.75 Lichen sclerosus et atrophicus. Haemorrhage and blistering may occur into the atrophic areas as in this patch on the back of her neck.

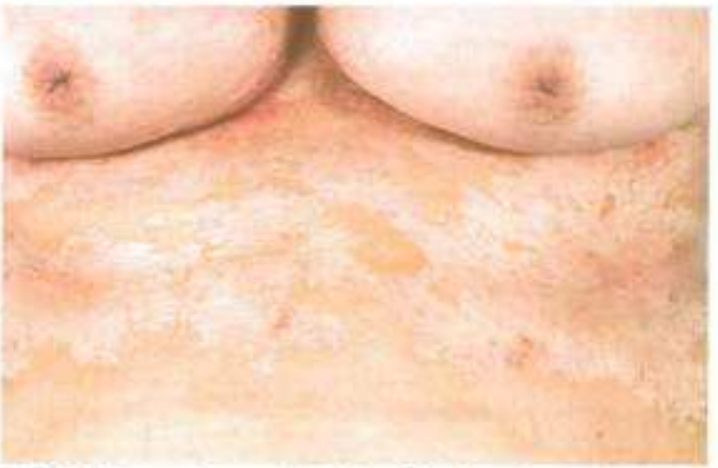


Fig. 21.76 Lichen sclerosus et atrophicus. Extensive extramucosal changes may occur in females, but rarely in males. Small foci of telangiectasia and haemorrhage are present.

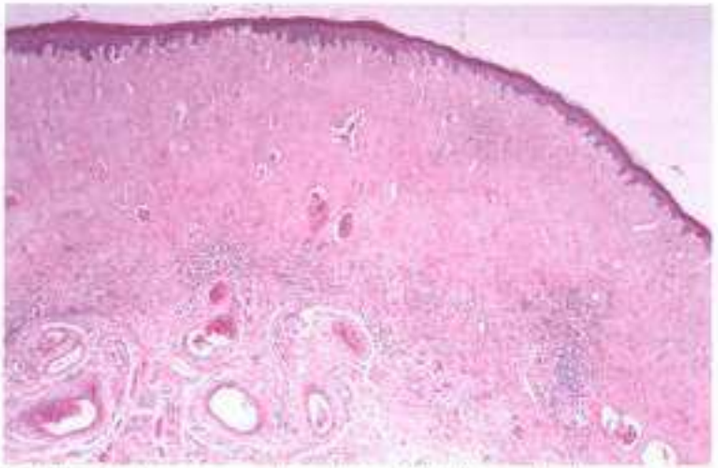


Fig. 21.77 Lichen sclerosus et atrophicus. Penile lesions showing hyperkeratosis, variable epidermal atrophy and irregular acanthosis. There is marked band-like hyalinization of the lamina propria and a chronic inflammatory cell infiltrate.

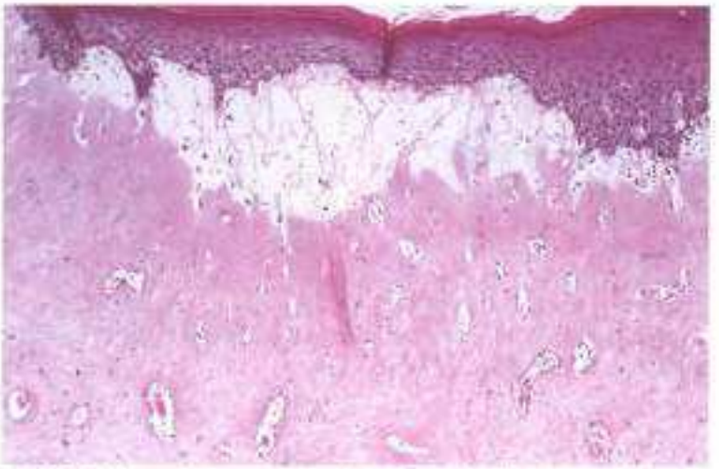


Fig. 21.78 Lichen sclerosus et atrophicus. Occasionally, intense oedema may result in subepidermal vesiculation. Ectatic blood vessels are conspicuous. This accounts for haemorrhagic bullous lesions.

Management

The extramucosal lesions are typical but a biopsy of genital lesions helps to exclude premalignant change in females. The histology of lichen sclerosus shows hyperkeratosis, variable epidermal atrophy and acanthosis (Fig. 21.77), basal cell hydropic degeneration and hyalinization of the lamina propria or superficial dermis. There is a chronic inflammatory cell infiltrate, blood vessel ectasia and, in severe disease, subepidermal vesiculation (Fig. 21.78).

The differential diagnosis is discussed in Chapter 28. Vulval lesions may be very itchy and superpotent glucocorticosteroids can be quite effective. Testosterone applied topically has been used in the past but side-effects of androgenization (hirsutism, deep voice, hair loss and cliteromegaly) are common and unacceptable.

Relapsing polychondritis

An episodic autoimmune inflammation of cartilaginous tissue that leads to fibrosis and destruction, sometimes also affecting the joints and the eyes.

Aetiology

It is uncommon, affects both sexes and usually commences in the fifth decade. It is debilitating, potentially life threatening and characterized by recurrent, often frightening episodes of inflammation of collagenous tissues, particularly the elastic tissue of the nose and ears, hyaline of peripheral joints, fibrocartilage of axial sites and the cartilage of the tracheobronchial tree and other proteoglycan-rich structures, for example the eye.

heart, blood vessels and inner ear. There is linkage to HLA-DR4 and occasionally association with other autoimmune diseases, such as hypothyroidism, systemic LE, rheumatoid arthritis, Behçet's syndrome, Sjögren's syndrome and mixed connective tissue disease. There are antibodies to type II collagen, large amounts of which are found in cartilage. Immunofluorescence of affected cartilage shows granular deposits of IgG, IgA, IgM and C3 to be present, suggesting it is an immune complex disorder. It is occasionally associated with the myelodysplastic syndrome.

Clinical Features

Symptoms

The majority present with episodic and recurrent attacks of redness, tenderness, warmth and swelling of the cartilaginous part of the external ear. Each attack lasts up to 2 weeks, but the frequency varies.

Morphology and distribution

One or both ears are swollen, red and painful (Fig. 21.79). The inferior soft lobule, which lacks cartilage, is spared. Ultimately, destruction occurs and floppy or cauliflower ears are typical. Hearing may be impaired.

Systemic features

The patient suffers lethargy, weight loss and fever. There may be a vasculitis, the leucocytoclastic variety affecting the skin or the polyarteritis type affecting internal organs.

Management and Course

The disorder can affect any cartilaginous structure, especially the joints, nose, ears, eyes, costochondral junction and larynx. The majority have a seronegative arthritis that affects one or several large or small joints. The degree of destruction to other organs varies, but at least a third die, usually as a result of laryngotracheal involvement, which initially produces cough, dyspnoea and wheezing but ultimately leads to airway collapse or obstruction.

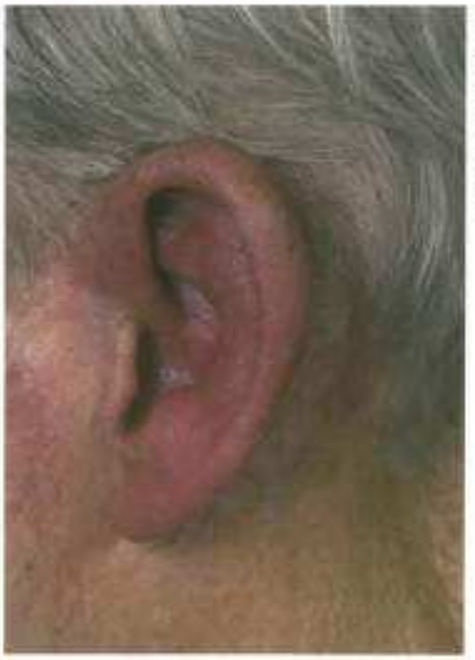


Fig. 21.79 Relapsing polychondritis. The upper helix is thickened but the lobe is spared. This man suffered episodic attacks of redness, pain and swellings. (Courtesy of Dr A. C. Pembroke.)

There is no specific test but three out of the six symptoms of bilateral auricular chondritis, non-erosive seronegative inflammatory arthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis and audiovestibular damage suggest the diagnosis. Histologically, there is loss of the normal basophilia of cartilage and an inflammatory infiltrate followed by fibrosis. The ESR and white cell count are elevated and there may be anaemia. Systemic steroids usually control the acute inflammatory episodes. Methotrexate, azathioprine, cyclophosphamide and dapsone are also used.

The skin and systemic disease 22

Sarcoidosis

A multisystem non-caseating granulomatous disease of unknown aetiology, which may represent an exaggerated immune response in a genetically susceptible individual to an exogenous or autoantigenic stimulus.

Aetiology

Although an infectious cause has been suspected (possibly caused by tuberculosis in a transmuted form), none has been proven. It is more common in developed countries and among certain races, in particular the Irish, West Indian (in London) and Puerto Rican (in New York). It is not a socio-economic disorder. Cell-mediated immune responses to tuberculin and other intradermal allergens such as *Candida* and *Trichophyton* proteins, mumps and dinitrochlorobenzene are suppressed. The humoral system is overactive. There is a predominance of $CD4^+$ helper T cells (TH_1), producing large amounts of γ-interferon and IL2 leading to B cell stimulation and hypergammaglobulinaemia. Monocytes are attracted from the circulation and epithelioid granulomas are formed. Granulomas are composed of macrophages and epithelioid cells surrounded by lymphocytes. They develop in order to confine pathogens, restrict inflammation and protect surrounding tissues. Non-caseating epithelioid granulomas occur in the absence of organisms or particulate matter. Helper T cells (TH_2) are relatively inactive and TH_2-associated cytokines are proportionately lower. Sarcoidal-like reactions occur in tattoos in patients treated with interferon and ribavirin for chronic hepatitis C, which may be explained because interferon facilitates TH_1 differentiation by suppressing TH_2 activation. Immune complexes are usually demonstrable, particularly in erythema nodosum, polyarthritis and uveitis. It occasionally occurs in families, especially monozygotic twins, and *HLA-DRB1* and *HLA-DqB1* are consistently reported as positive. There is an association with a butyrophilin-like 2 (*BTN L2*) gene on chromosome 6.

The disorder predominantly affects younger adults. Any organ may be involved, but especially the lungs, eyes, liver, spleen, lymph nodes, bone, nervous system and skin.

Clinical Features

Symptoms result from invasion, replacement, pressure and fibrosis. Anaemia and hypercalcaemia may occur. Sarcoidosis may affect the skin either alone or in association with systemic disease and the extent of involvement of the skin does not correlate with that systemically. Sarcoidosis may present in the skin in a variety of ways:

- erythema nodosum
- granulomatous infiltrates of the skin
- granulomatous invasion of old scar tissue
- lupus pernio
- annular sarcoidosis of the face
- clinically distinct lesions in black skins.

Erythema nodosum

Erythema nodosum (Löfgren's syndrome, Ch. 18) is the commonest. It is associated with fever and arthralgia and has an acute onset. There are usually no pulmonary symptoms, but a chest radiograph reveals bilateral hilar lymphadenopathy, which is sufficiently characteristic to confirm the diagnosis. Biopsy of the hilar glands shows a non-caseating granulomatous infiltrate. The prognosis is excellent, with clearing of the chest radiograph changes within a couple of years.

Granulomatous infiltrates of the skin

Many of these patients have pulmonary involvement, lymphadenopathy and splenomegaly.

Morphology

Persistent infiltrated papules, nodules (Fig. 22.1) and plaques are the most usual changes. Annular configurations (Fig. 22.2) are common.

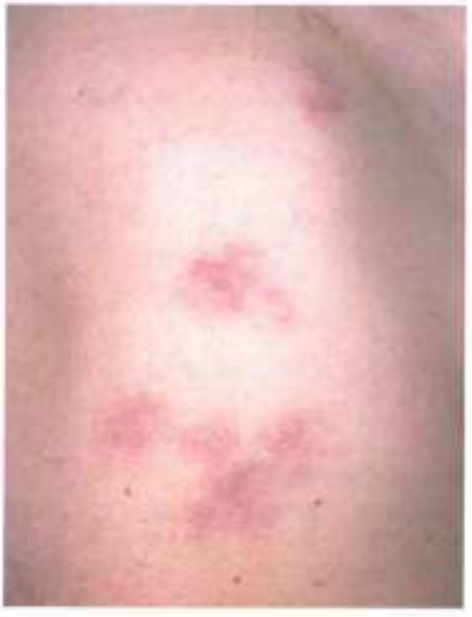


Fig. 22.1 Sarcoidosis. The nodules are red-brown or purple and have a smooth surface.

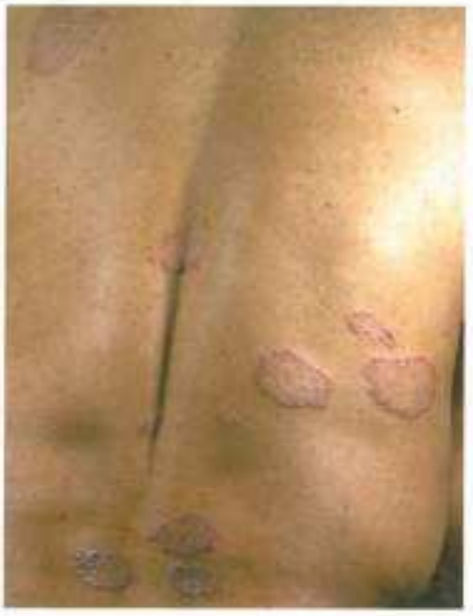


Fig. 22.2 Sarcoidosis. The purple plaques often have an annular configuration. The trunk is a common site.

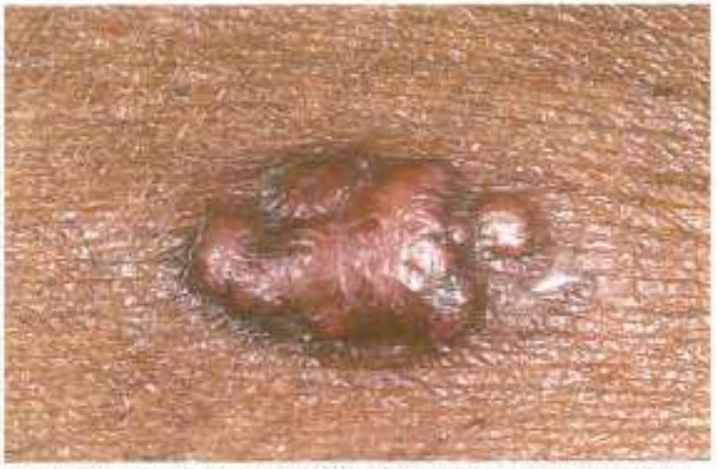


Fig. 22.3 Sarcoidosis. Common in Afro-Caribbeans, the plaques often have a red-brown colour.

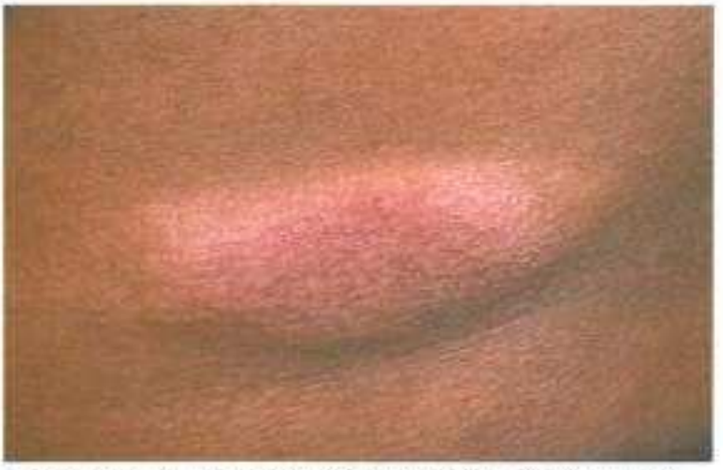


Fig. 22.4 Sarcoidosis. The lesions may be subcutaneous and the colour less striking. A biopsy is the easiest route to the diagnosis.

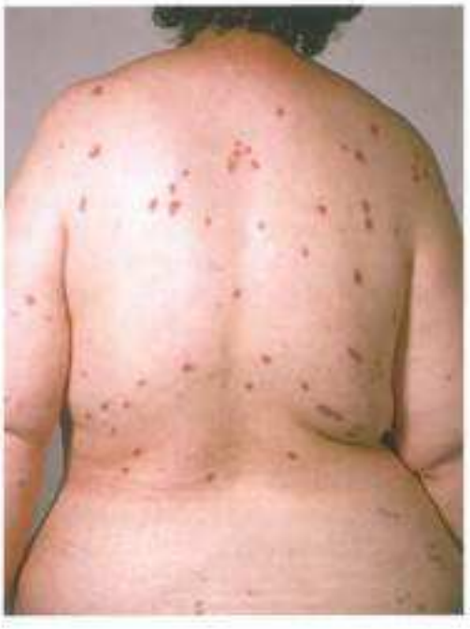


Fig. 22.5 Sarcoidosis. Widespread plaques may occur on the trunk.

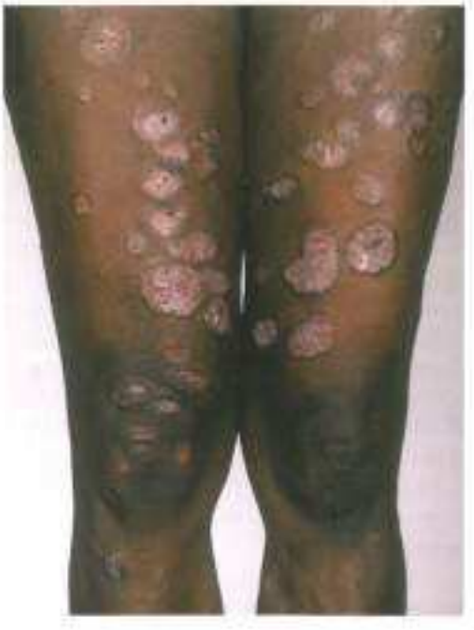


Fig. 22.6 Sarcoidosis. Bilateral granulomatous annular plaques are present on the limbs. Most of these patients have pulmonary involvement, lymphadenopathy and splenomegaly. African-Americans and Afro-Caribbeans are affected three times more commonly than Caucasians.

They may be red-brown (Fig. 22.3) or purple in colour and are usually smooth surfaced since the pathology is in the dermis or subcutaneous tissue (Fig. 22.4) without any epidermal involvement.

Distribution

Anywhere on the body, but the trunk (Fig. 22.5), limbs (Fig. 22.6) and face (Figs 22.7 and 22.8) are common sites. The lesions are often bilateral.

Granulomatous invasion of old scar tissue

This is particularly characteristic. Previously atrophic scars may become livid and purple in colour including at previous Mantoux sites.

Lupus pernio

First described by Besnier in 1889, it is slightly more common in older patients and is usually associated with chronic fibrotic sarcoid in other tissues including the lungs, upper respiratory tract, kidneys and lacrimal glands. Bone cysts and chronic uveitis are common.

Morphology

This is a chronic, persistent and indolent variant. The initial lesions are papules or nodules but may become exuberant plaques, with a rather cyanotic hue.

Distribution

Lesions occur on the nose (Fig. 22.9), cheeks (Fig. 22.10) and ears (Fig. 22.11). Nasal destruction may occur.

Annular sarcoidosis of the face

Annular configurations are common in sarcoid but there is a variety occurring on the forehead (Fig. 22.12), face and neck where the central area may become depigmented and scarred. It can be distinguished histologically from facial and scalp necrobiosis lipoidica.

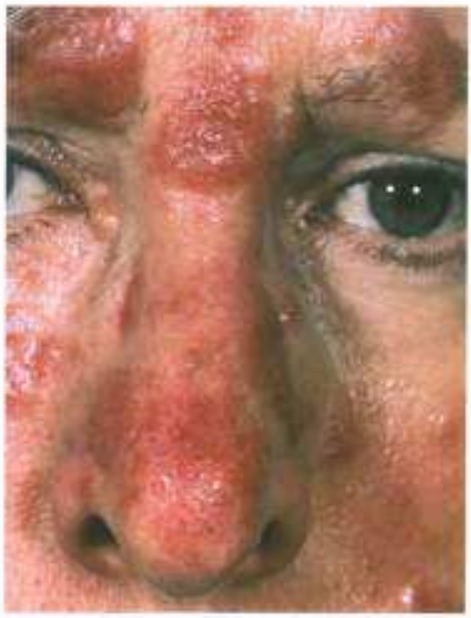


Fig. 22.7 Sarcoidosis. Red-brown nodules and plaques are present. There are invariably sarcoidal lesions present in other organs. Systemic steroids and other immunosuppressants are required for disfiguring disease such as this.

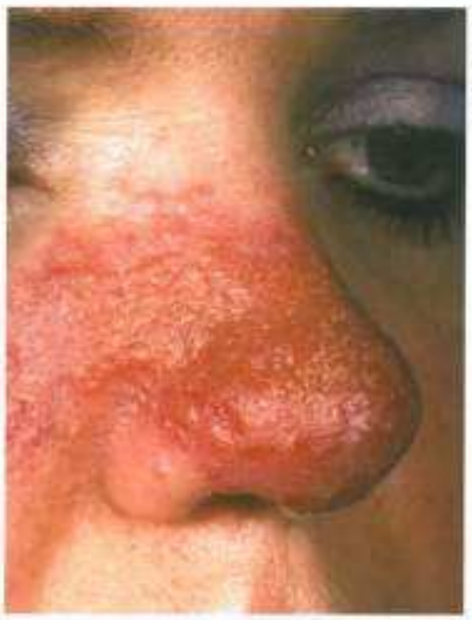


Fig. 22.8 Sarcoidosis. The nose and cheeks may be infiltrated by red-brown papules that become confluent.

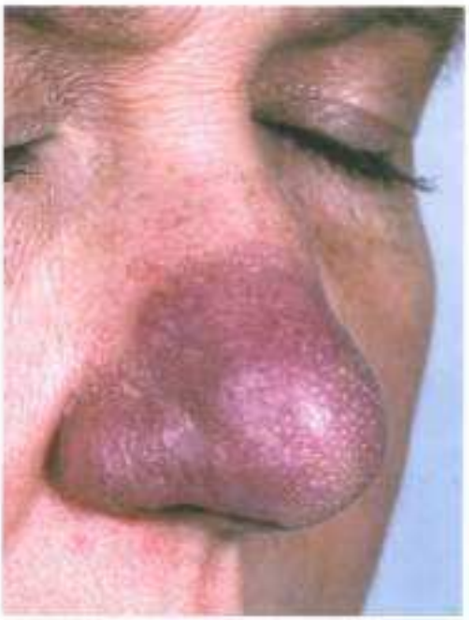


Fig. 22.9 Lupus pernio. The purple colour of the infiltration is distinctive. It is disfiguring and may be destructive (hence lupus). It may respond to laser therapy.

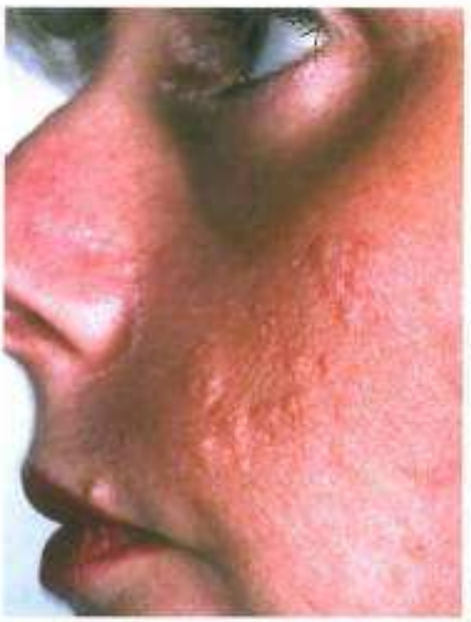


Fig. 22.10 Sarcoidosis. The lesions of sarcoidosis may be quite small. These are firm flesh-coloured papules. Biopsy is critical in dermatology for establishing the diagnosis.

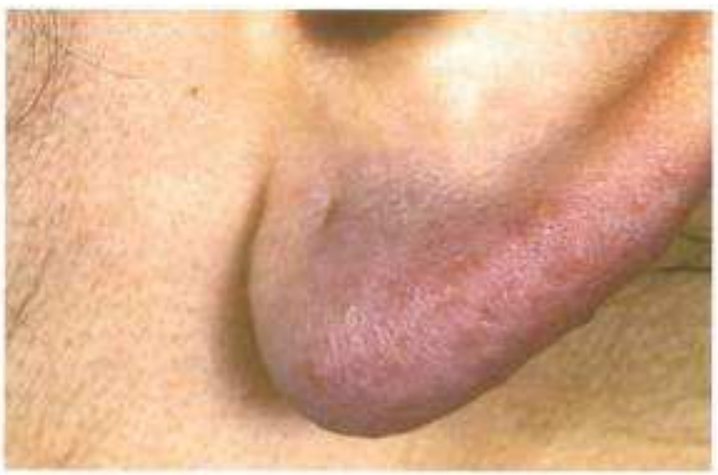


Fig. 22.11 Lupus pernio. The cyanotic hue is characteristic. The earlobes, nose and cheeks are affected areas most prone to perniosis.

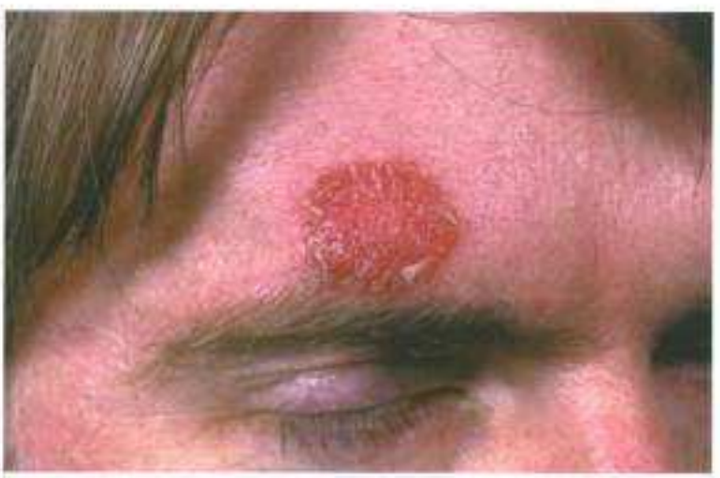


Fig. 22.12 Sarcoidosis. A facial red plaque may mimic necrobiosis lipoidica, but the histology distinguishes between the two.

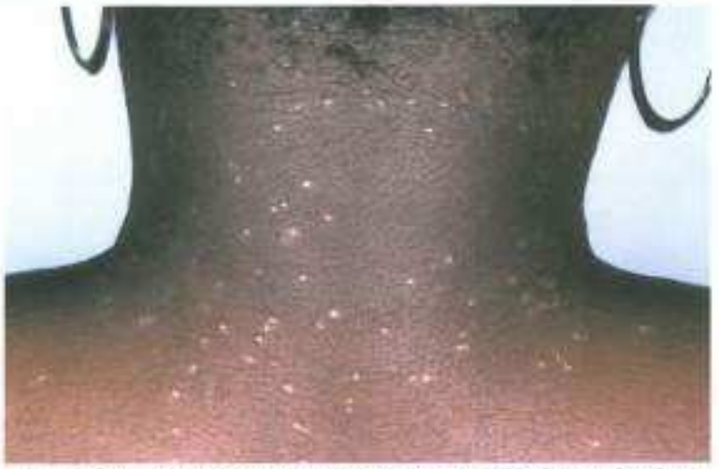


Fig. 22.13 Sarcoidosis. Small firm hypopigmented papules occur in black skins which may easily be overlooked but should be biopsied.

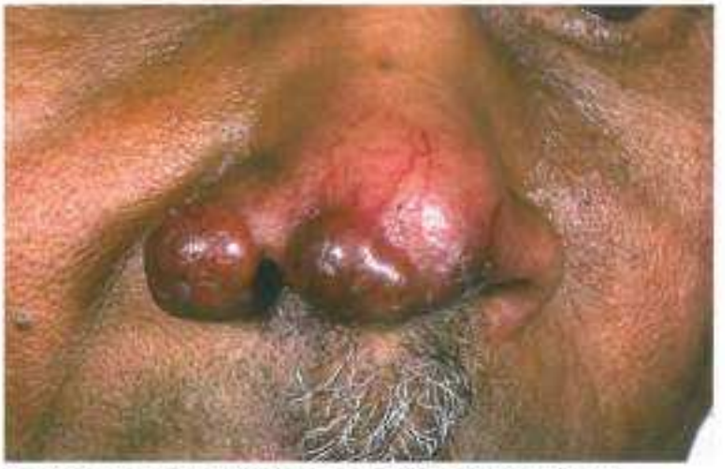


Fig. 22.14 Sarcoidosis. In West Indians, the red-brown nodules occur particularly around the nose.

Sarcoidosis in black skin

Morphology

Brown papules or nodules occur with a smooth surface. Sometimes there are only hypopigmented papules (Fig. 22.13).

Distribution

The papules occur around the eyelids and nose (Fig. 22.14) and may be extremely disfiguring and simulate lupus pernio. Similar nodules may occur in the skin of the phalanges (Fig. 22.15), particularly the terminal, and are associated with cystic bone changes in radiographs.

Systemic signs of sarcoidosis

There are a number of systemic signs:

- the patient may suffer lethargy, malaise, anorexia and weight loss
- a cholestatic syndrome of pruritus, jaundice and occasionally portal hypertension and hepatic failure
- pulmonary involvement ranges from benign hilar adenopathy associated with erythema nodosum to pulmonary infiltrates with cough, breathlessness and diminution of respiratory function. Aspergillosis may complicate pulmonary fibrosis.
- the nervous system may be involved with cranial nerve palsies, various hypothalamic syndromes or meningoencephalitis; VIIth nerve palsy, fever and parotitis is known as *Heerfordt's syndrome*
- bone changes are usually symptomless but occur in a substantial number of patients as cysts on the hands and feet
- the joints may be acutely affected in association with erythema nodosum or form part of a chronic polyarthritis
- a proximal myopathy is not uncommon
- cardiomyopathy and conduction defects may occur. Heart block may cause sudden death, if not recognized and treated with a pacemaker. An automatic implantable cardioverter defibrillator may be required for arrhythmias.
- the eye changes comprise an acute uveitis associated with erythema nodosum or chronic uveitis, conjunctivitis or kerato-conjunctivitis sicca (Sjögren's syndrome). Chronic anterior uveitis may lead to glaucoma and loss of vision. Posterior uveitis may be associated with CNS involvement.
- the kidneys may be involved either directly or as part of hypercalciuria or hypercalcaemia.

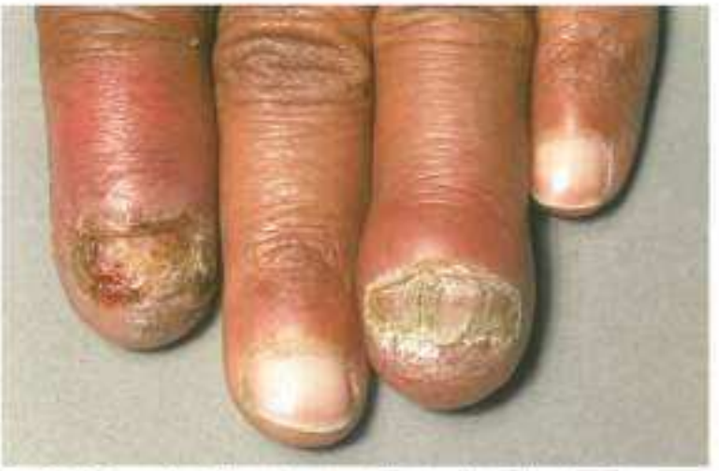


Fig. 22.15 Sarcoidosis. Granulomatous infiltration of the skin and subcutaneous tissues occurs in the phalanges, with the destruction of the nails.

Management

The diagnosis is based on the clinical, radiological and histological findings. A non-caseating granulomatous infiltrate composed of epithelioid cells with occasional giant cells is present (Fig. 22.16). Special stains for tubercle bacilli and fungi are negative. The angiotensin converting enzyme (ACE) is positive in 60% (but also is positive in diabetes mellitus and alcoholic liver disease). It is thus non-specific and insensitive and a poor therapeutic guide.

The Kveim test is an intradermal injection of a suspension of sarcoid tissue, usually from the spleen of an affected individual; which, if positive, is followed 4–6 weeks later by the formation of epithelioid cell granulomas. This test, however, is less frequently used than formerly in view of concerns about the possible transmission of viral infections, particularly human immunodeficiency virus (HIV). Biopsy of affected tissue is the most useful means of establishing the diagnosis. MRI and PET scans are useful to assess extent of systemic involvement.

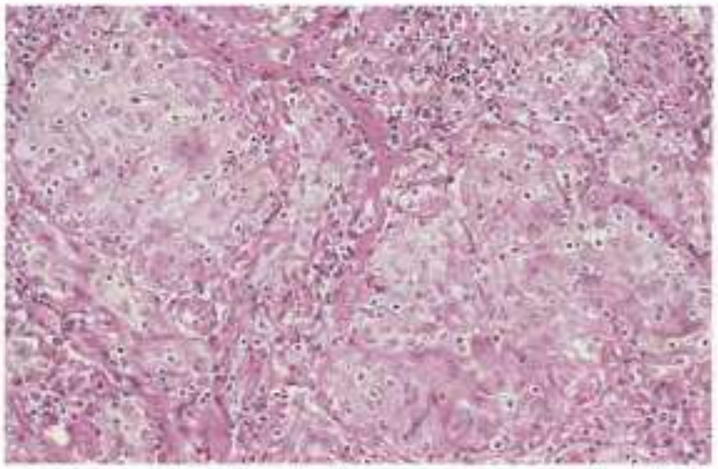


Fig. 22.16 Sarcoidosis. The section shows an extensive granulomatous infiltrate composed of well-defined clusters of epithelioid cells with occasional giant cells. Early scarring is seen in the centre of the field.

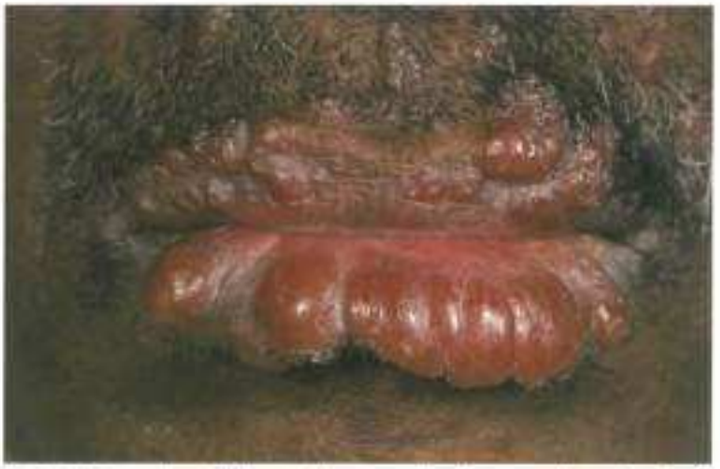


Fig. 22.17 Sarcoidosis. These red-brown granulomatous papules and nodules in the lips are very characteristic. (Courtesy of Dr Andrew Pembroke.)

Two-thirds have remission within a decade. One-third have unrelenting disease. The prognosis depends on the extent and the site of systemic involvement. The cutaneous changes do not give rise to any symptoms other than disfigurement, although this may be severe enough to require active therapeutic intervention.

Clearly sarcoidosis requires a multidisciplinary approach. It is not easy to treat. Systemic steroids are the mainstay of therapy but other steroid-sparing agents, such as methotrexate, mycophenolate mofetil, thalidomide, adalimumab and antimalarial drugs (Figs 22.17 and 22.18), are used. Cutaneous lesions may be infiltrated with triamcinolone. Photodynamic therapy may also be effective.

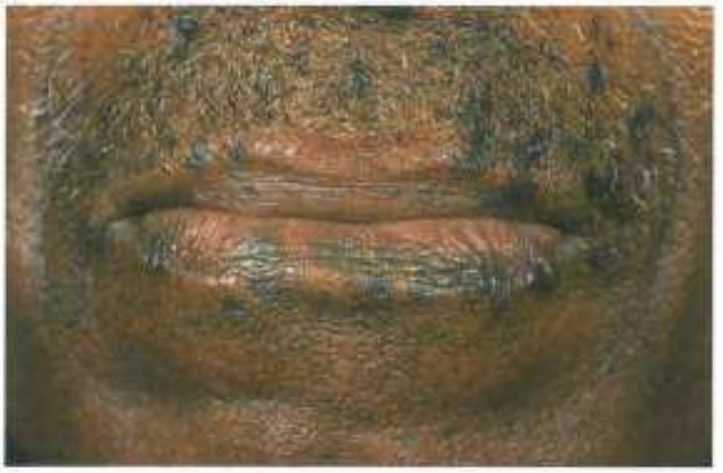


Fig. 22.18 Sarcoidosis. The lesions in Fig. 22.17 responded to treatment with mepacrine. It does however produce a temporary yellow-brown discoloration of the skin. (Courtesy of Dr Andrew Pembroke.)

Mastocytosis

A heterogeneous collection of disorders characterized by the proliferation and accumulation of mast cells in various organs and in particular the skin.

Aetiology

Mast cells originate from pluripotential bone marrow progenitor cells that express CD34. They are present in the bone marrow, throughout the connective tissue, particularly concentrated near epithelial surfaces, in and around peripheral nerves and adjacent to blood and lymphatic vessels. They have a distinctive oval or round, darkly staining nucleus with a moderate amount of cytoplasm, rather resembling a fried egg. There are tiny granules in the cytoplasm that show metachromasia with Giemsa or toluidine blue. They secrete a number of pharmacological substances, including histamine, slow-reacting substance of anaphylaxis, prostaglandin D_2, platelet-activating factor, eosinophilotactic factors, neutrophil chemotactic factor, acid hydrolases and heparin. Mast cells, like basophils, have cell membrane-bound IgE antibody and may be triggered to release these substances in response to stimulation by either specific antigens or a number of non-immunological chemical mast cell degranulators (including alcohol, morphine and codeine).

Circulating mast cells express not only CD34, but also the tyrosine kinase KIT (CD117), and IgG receptors (FcγR II), but not high affinity IgE receptors (FCεRI). Two amino acid mutations have been described in codons 816 and 560, which result in activation of the cKIT protein, a proto-oncogene on chromosome 4q12, which encodes the tyrosinase kinase receptor for stem cell factor (SCF), an important growth factor for mast cells and prolongs cellular survival by inhibiting apoptosis.

The WHO classification recognizes seven types of mastocytosis:

- Cutaneous – nodular, maculopapular and diffuse
- Indolent systemic, where cutaneous is the dominant feature
- Systemic mastocytosis associated with a clonal haematological non-mast cell lineage disease, e.g. myelodysplastic syndrome
- Aggressive systemic mastocytosis
- Mast cell leukaemia
- Mast cell sarcoma
- Extracutaneous mastocytoma.

The majority of patients with mastocytosis have a disorder confined to the skin with an excellent prognosis.

Clinical Features

There are four cutaneous variants of mastocytosis:

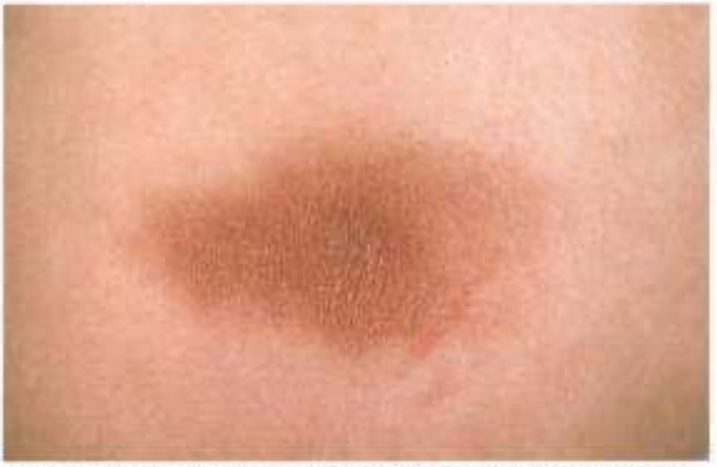


Fig. 22.19 Localized mastocytoma. There is a brown plaque that will urticate (go red and itch) with trauma. It occurs in infancy, may be single or multiple and disappears spontaneously.

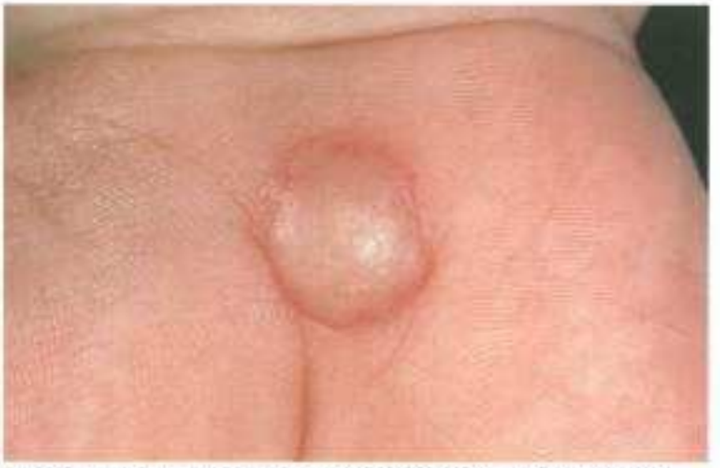


Fig. 22.20 Localized mastocytoma. A mastocytoma is a benign tumour of mast cells. This one on the palm has blistered in response to rubbing. He was 2 months old.

Localized mastocytoma

Symptoms

Presentation occurs in infancy as a lesion that becomes red and itches when rubbed. There is occasionally generalized flushing.

Morphology

A red-brown plaque (Fig. 22.19) or nodule which urticates when rubbed (Darier's sign) or blisters (Fig. 22.20) spontaneously.

Distribution

The trunk or extremities.

Telangiectasia macularis eruptiva perstans

Symptoms

Widespread rash in an adult, which itches with rubbing.

Morphology

There are confluent areas of telangiectatic macules on an erythematous background with hyperpigmentation (Fig. 22.21). There may be scattered papules that simulate urticaria pigmentosa.

Distribution

Anywhere on the skin.

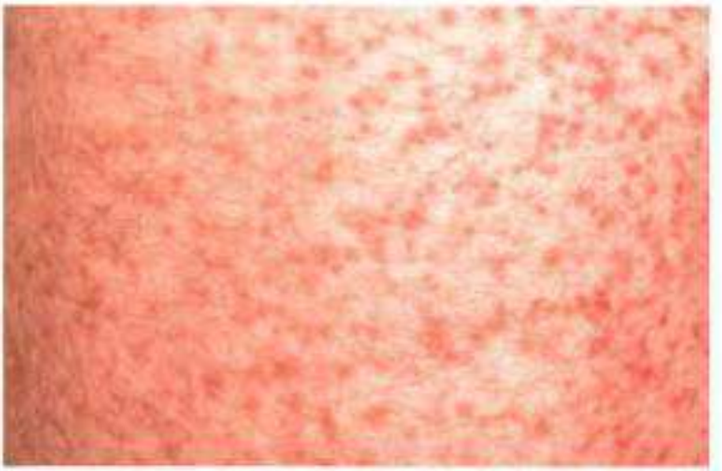


Fig. 22.21 Telangiectasia macularis eruptiva perstans. In adults, the lesions may be persistent red-brown macules, often with telangiectasia. It is quite benign.

Urticaria pigmentosa

Symptoms

Half present in infancy (Fig. 22.22). The mother may notice whealing of the skin, particularly after bathing. The remainder commence in adult life.

Morphology

The red-brown macules redden and swell (urticate) with stroking individual lesions (Fig. 22.23). Blistering may predominate (Fig. 22.24).

Distribution

The trunk (Fig. 22.25) and limbs (Fig. 22.26) may be extensively affected.

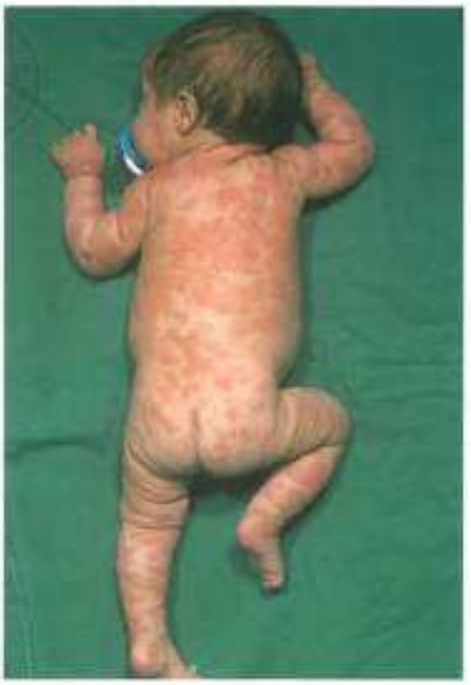


Fig. 22.22 Urticaria pigmentosum. There are urticated red-brown lesions scattered widely over the body and limbs. This type, which develops in infancy, invariably clears spontaneously.

Diffuse and erythrodermic mastocytosis

Symptoms

Blistering in a neonate whose skin was normal at birth.

Morphology

The blisters resemble those of pemphigoid and there is generalized thickening of the skin, often with visible oedema and accentuation of the skin

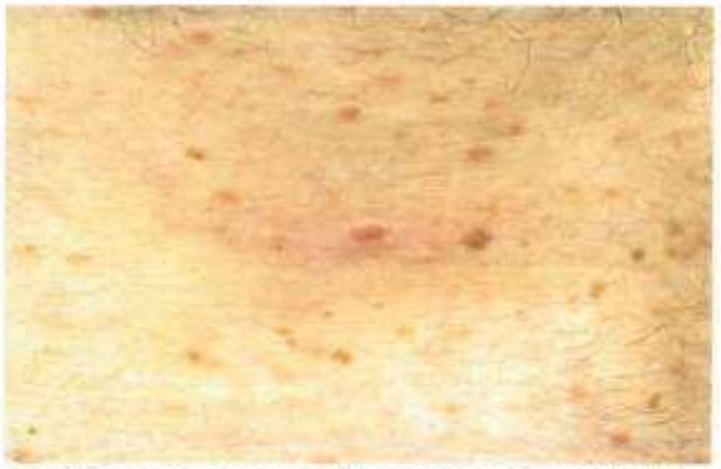


Fig. 22.23 Urticaria pigmentosum. There are widespread, pigmented patches and plaques, which go red (central lesion) with rubbing (Darier's sign). It is harmless and disappears spontaneously within 2 or 3 years.

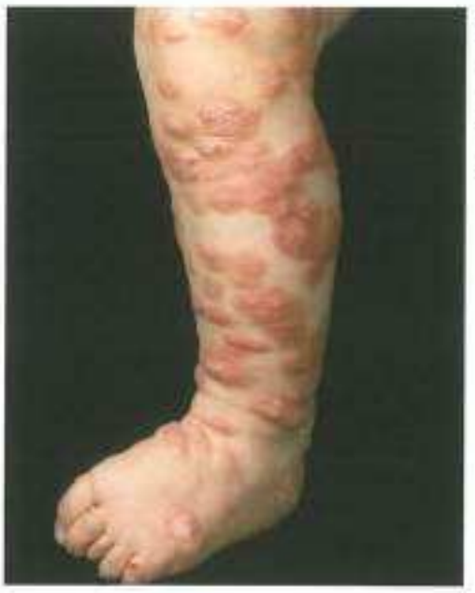


Fig. 22.24 Urticaria pigmentosum. A generalized bullous variety does occur in infants, which is distressing but the outlook is good.

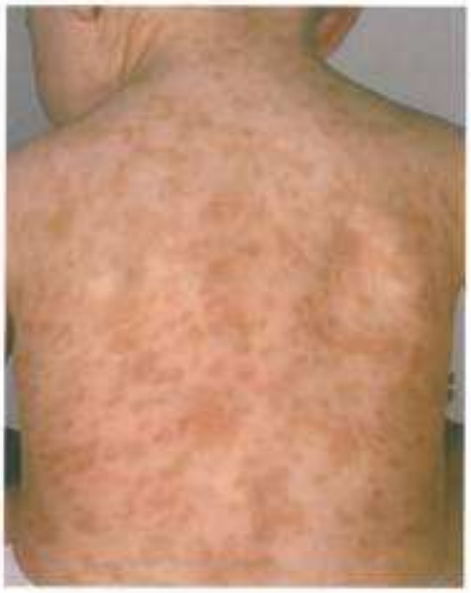


Fig. 22.25 Urticaria pigmentosum. There is a red, urticarial papule in the centre of a field of pigmented macules, hence the name urticaria pigmentosum.

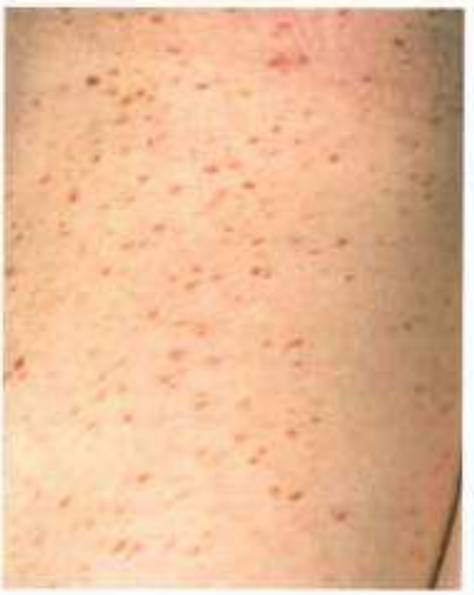


Fig. 22.26 Urticaria pigmentosa. The trunk and limbs are involved. This maculopapular type in adults occasionally develops indolent systemic features with raised serum tryptase, cKit mutation and urinary N-methyl histamine levels.

markings. The skin surface may be smooth or covered with minute papules, giving it a *peau d'orange* appearance, and be bright red or hyperpigmented.

Distribution

The eruption is extensive. Although usually the condition resolves spontaneously, there may be complications because of the enormous mast cell load, including hypotension and severe diarrhoea.

Systemic features

Acute episodes of flushing, wheezing, diarrhoea, hypotension and shock may result from release of mast cell mediators. Anaemia, headaches, diarrhoea, weight loss, tachycardia, weakness and bone involvement are chronic symptoms.

Management

A skin biopsy is necessary. Lidocaine should be injected without epinephrine (adrenaline) away from the lesion itself to avoid degranulation. Numerous mast cells with intensely eosinophilic cytoplasm and small hyperchromatic nuclei are present in the dermis (Fig. 22.27). They contain metachromatic granules that stain with toluidine blue.

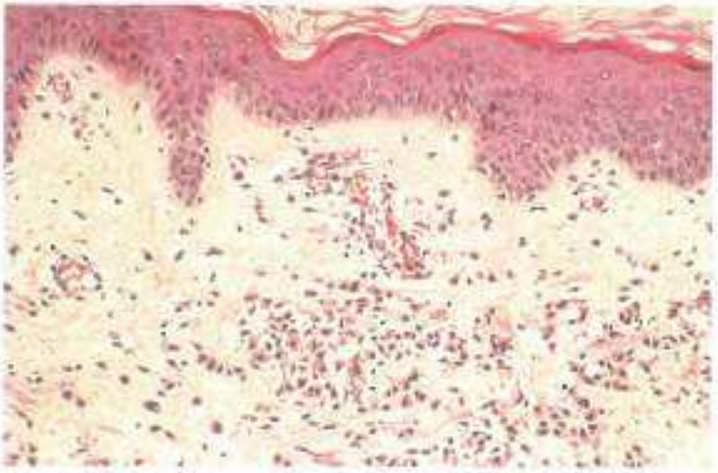


Fig. 22.27 Urticaria pigmentosa. Numerous mast cells with intensely eosinophilic cytoplasm and small, uniform, hyperchromatic nuclei are present in the dermis.

The treatment of cutaneous forms is largely symptomatic. The localized and infantile forms usually resolve spontaneously. If the solitary lesion does not clear, it can be excised. Antihistamines, disodium cromoglycate and ketotifen are the mainstay of therapy for pruritus.

Photochemotherapy has been used for those adults bothered by the persistence of cosmetically unacceptable extensive lesions. Superpotent topical steroids and mast cell stabilizing agents such as disodium cromoglycate may be helpful. Alcohol and other mast cell degranulating agents should be avoided.

Systemic involvement is rare and occurs in middle-aged patients with chronic urticaria pigmentosa. Heparosplenomegaly, radiographic evidence of bone involvement and haematological abnormalities predominate. The SCORMA (SCORing MAstocytosis) index may be helpful in determining the likelihood of systemic involvement and is based on (a) the extent, (b) the severity of the lesions, (c) the symptomatology, and is proportional to the level of serum tryptase. CD117 is positive and the cKit mutation D816V is found. The latter may be inhibited by imatinib or dasatinib, but results are mixed. The condition may be fatal.

Carcinoid syndrome

A syndrome of episodic flushing, diarrhoea, right-sided heart valve abnormalities, telangiectasia, asthma, paroxysmal hypotension and pellagra and results from the release of serotonin (5-hydroxytryptamine) and other agents by a slow-growing malignant tumour.

Aetiology

Carcinoid tumours are rare and occur in either sex at any age but usually latterly. They arise from cells that have cytoplasmic granules with an affinity for silver (argentaffin), usually in the intestinal mucosa, in the region of the ileocaecal valve. Those in the appendix rarely, if ever, metastasize but those in the ileum, caecum, colon and stomach may metastasize to the liver and regional lymph nodes. Ovarian and bronchial carcinoid tumours also occur. They are usually benign but occasionally metastasize.

Serotonin, a smooth muscle stimulant, is secreted from these cells together with the vasodilator bradykinin, histamine and adrenocorticotrophic hormone (ACTH). These account for the symptoms. In addition, there is a disturbance of tryptophan metabolism. Usually 1% of tryptophan is metabolized by the serotonin pathway but in the carcinoid syndrome, 60% is shunted through it; as a result, less niacin and protein are formed from tryptophan and pellagra occurs in addition to the diarrhoea.

Clinical Features

Symptoms

Episodic spontaneous flushing is precipitated by emotional or physical stimuli including alcohol, certain foods (red wine, chocolate and blue cheese) and defaecation. Initially, it is brief and acute in onset but increases in duration and frequency so that ultimately a permanent state of hyperaemia results.

Morphology

The facial capillaries may be dilated and gross telangiectasia may occur. Oedema including periorbital may be present. Latterly a pellagra-like pigmentation and scaling and sclerodermatoid changes may result.

Distribution

Flushing and telangiectasia occurs predominantly on the face and neck initially and extend to the chest, arms and shoulders. The pigmentation of pellagra occurs in a light-exposed distribution, particularly the face and neck and dorsal surfaces of the hands, arms and feet.

Systemic features

Bronchospasm, right-sided cardiac dysfunction, hypotension, peptic ulceration and diarrhoea.

Management

The differential diagnosis of the causes of flushing includes physiological, menopausal, rosacea, thyrotoxicosis, drugs and various tumours. The common drugs include vasodilators (e.g. nitroglycerin), calcium channel blockers (e.g. nifedipine), disulfiram (including procarbazine and alcohol), tamoxifen, opiates, antiandrogens, calcitonin, ciclosporin, anticancer drugs (e.g. doxorubicin), antibiotics (e.g. vancomycin, rifampicin), alcohol, chlorpropamide and alcohol, buserelin for prostatic cancer, ACE inhibitors, metronidazole, food additives (monosodium glutamate and sulphites) and radiographic contrast media.

The tumours causing flushing are carcinoid syndrome, mastocytosis, phaeochromocytomas, pancreatic tumours secreting vasoactive intestinal peptides, renal cell carcinoma, medullary carcinoma of the thyroid, basophil chronic granulocytic leukaemia and CNS tumours (e.g. colloid cyst, third ventricle).

Flushing may be wet (mediated by autonomic nerves, which also control eccrine sweat glands) or dry (direct action on the vascular smooth muscle and, therefore, no increase in sweating). The other causes of the pellagra dermatosis are dietary deficiency of niacin or tryptophan, the ingestion of certain drugs (isoniazid, 5-fluorouracil, 6-mercaptopurine or sulphapyridine) and Hartnup's disease. The diagnosis can be made by measuring 5-hydroxyindoleacetic acid (the major metabolic of serotonin) levels in the urine. Blood and urinary levels of serotonin are increased. Surgery is the treatment of choice if possible.

Octreotide inhibits hormone secretion by the carcinoid cells and is effective in the management of acute manifestations; long-acting preparations of other somatostatin analogues may be used for chronic symptoms.

The histiocytoses

There are three types of cell (Langerhans' cells, mononuclear cells/macrophages and dermal dendrocytes) which arise from a common progenitor cell in the bone marrow.

Langerhans' cells are potent antigen-presenting cells, which migrate to and from the epidermis (including hair follicles). They are S100, CD45, CD101 and CD1a-positive (specific for Langerhans' cells) and exhibit Birkbeck granules in their cytoplasm. They play an important role in immunosurveillance. After being triggered by a new antigen they migrate to regional lymph nodes and activate antigen-specific T cells which return to the skin and participate in the inflammatory response against the antigen via chemokines and cytokines. Dysfunction gives rise to Type I Langerhans' cell histiocytosis.

Neutrophil/macrophage lineage progenitor cells in the bone marrow mature into circulating monocytes (regulated by colony-stimulating factors), which migrate into various tissues and differentiate into macrophages (known as histiocytes) which function as phagocytes or antigen-presenting cells. They may give rise to type II non-LC histiocytes, which in turn may transform into Type III malignant histiocytosis.

Type II histiocytosis may be primarily cutaneous and largely self-resolving (juvenile xanthogranuloma, benign cephalic histiocytosis and generalized eruptive histiocytomas), primarily cutaneous but often persistent and progressive (papular xanthoma), frequently systemic (necrobiotic xanthogranuloma, multicentric reticulohistiocytosis, Rosai–Dorfman

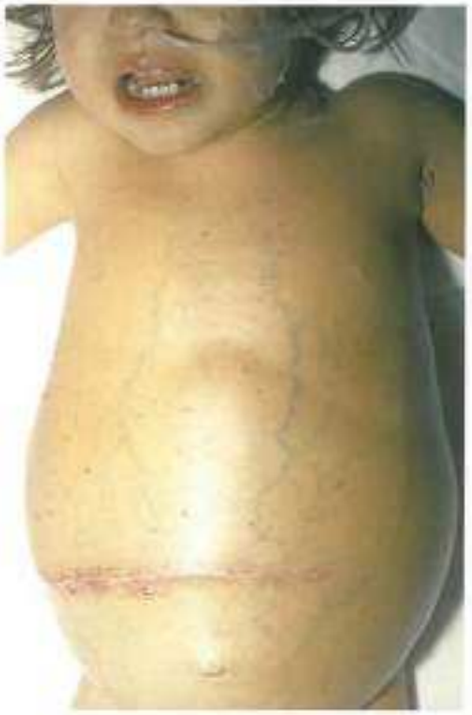


Fig. 22.28 Langerhans' cell histiocytosis. Children under the age of 2 with multisystem disease have a poorer prognosis. It is often known as Letterer–Siwe disease. This infant has jaundice, hepatomegaly, ascites and discrete purpuric papules.

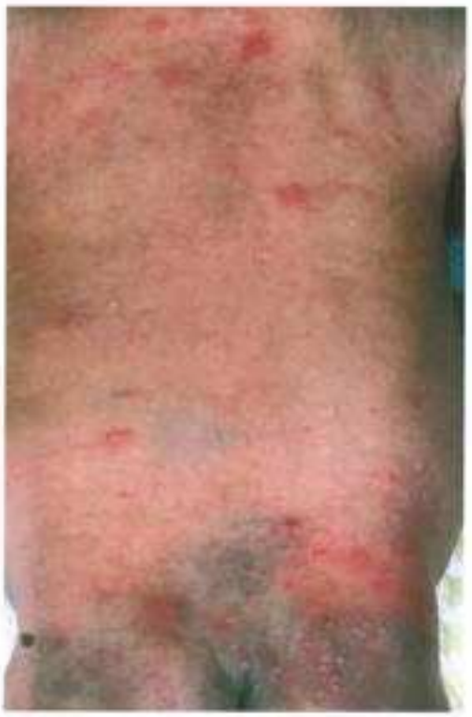


Fig. 22.29 Langerhans' cell histiocytosis. Here there are discrete red-brown papules scattered over the trunk. A biopsy is necessary for histopathology and immunostaining. CD1a is specific for Langerhans' cells.

and xanthoma disseminatum) and systemic with rare cutaneous involvement (Erdheim–Chester and haemophagocytic lymphohistiocytosis).

Type III malignant histiocytosis is a neoplastic proliferation of histiocytes involving the liver, spleen, lymph nodes and bone marrow. 10% have yellow papules or nodules. It is rapidly fatal without early chemotherapy and/or bone marrow transplantation.

LANGERHANS' CELL HISTIOCYTOSIS

A clonal proliferation of activated Langerhans' cells affecting a single (skin, bone or lymph node) or multiple systems, causing a spectrum of disease with distinctive clinical patterns in some cases and chronic immune dysregulation.

Aetiology

Langerhans' cell histiocytosis is a reactive condition in which abnormal but not malignant cells accumulate. The condition was known as histiocytosis X until the X was found to be Langerhans' cells. The proliferative cells are large (about four times the size of a small lymphocyte) and have distinctive reniform nuclei. Electron microscopy of these cells shows rod-shaped granules in the cytoplasm that are reminiscent of tennis racquets and are identical to those found in the Langerhans' cells. Proliferative granulomatous and xanthomatous histological patterns occur. The abnormal proliferation of Langerhans' cells has been considered as an altered response to an infection, possibly viral.

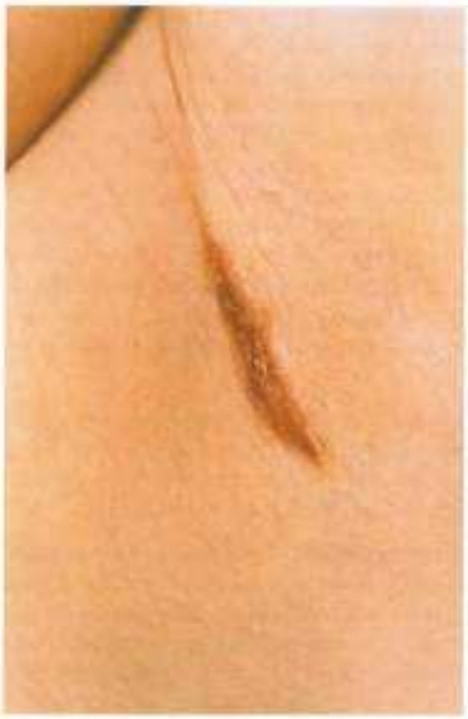


Fig. 22.30 Langerhans' cell histiocytosis. Linear patterns are characteristic, as here in the axilla. A skin biopsy establishes the diagnosis. (Courtesy of Dr Stephanie Munn.)

Clinical Features

There are four clinical patterns known as Letterer–Siwe disease, Hand–Schüller–Christian syndrome, eosinophilic granuloma of bone and self-healing reticulohistiocytosis. There is considerable overlap between them. The retention of the original names is useful, however, because they do have different features. Characteristic cutaneous lesions occur in the first two conditions.

- **Letterer–Siwe disease** is a disorder of infancy and has a tendency to an acute course. There is fever, anaemia, hepatosplenomegaly (Fig. 22.28), lymphadenopathy, pulmonary involvement and secondary infections, especially otitis media. There may be painful osteolytic lesions especially in the cranium and a destructive periodontitis due to osseous infiltration by proliferative cells. The latter leads to loss of periodontal support and floating teeth. The skin lesions are characteristic. Mortality is appreciable if the liver, lung or brain is involved. There are discrete yellow-brown papules, sometimes with a purpuric (Fig. 22.29) or necrotic element, which occur in crops, or linear arrangements (Fig. 22.30). They are distributed on the face, trunk,

Fig. 22.31 Langerhans' cell histiocytosis. Yellow-brown papules in the scalp may give rise to crusting, which is easily misdiagnosed as cradle cap.

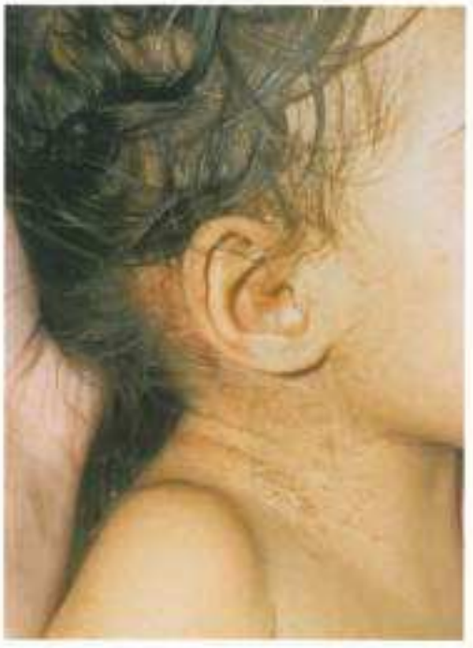


Fig. 22.32 Langerhans' cell histiocytosis. Closer inspection of the child in Fig. 22.31 reveals purpuric papules on the side of the neck. Skin biopsy revealed the true diagnosis.

scalp (Fig. 22.31), neck (Fig. 22.32), buttocks and napkin area (Fig 3.55).

- **Hand–Schüller–Christian disease** is a chronic progressive multifocal form occurring in children or young adults. The four main features are bony and mucocutaneous lesions, diabetes insipidus and exophthalmos (Fig. 22.33). However, many systems may be affected, particularly pulmonary and reticuloendothelial. The skin lesions are not quite as common as those of Letterer–Siwe disease. They are macules and papules, often with a petechial element and sometimes with a surface scale. Secondary infection is common and scarring may result. Nodules may be present, particularly on the scalp in association with bony defects. The distribution is the medial aspects of the chest and back, intertriginous folds, scalp and temporoparietal regions. Nodular ulcerative lesions may be found in the mucous membranes, particularly the gingiva and also the vulva.
- **Eosinophilic granuloma** occurs in children and young adults and presents as an isolated bony lesion, usually in the cranium. Sometimes multiple lesions are found. Cutaneous signs are unusual but are similar to those already described. The condition is usually benign.
- **Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease)** presents at birth or within the first days of life. The child is otherwise well. Cutaneous lesions predominate and usually resolve. They are solitary or an eruption of firm red papules or nodules, which sometimes ulcerate but regress within 3 months. The distribution is widespread but there is no involvement of the mucous membranes. Occasionally solitary lesions occur on the face.

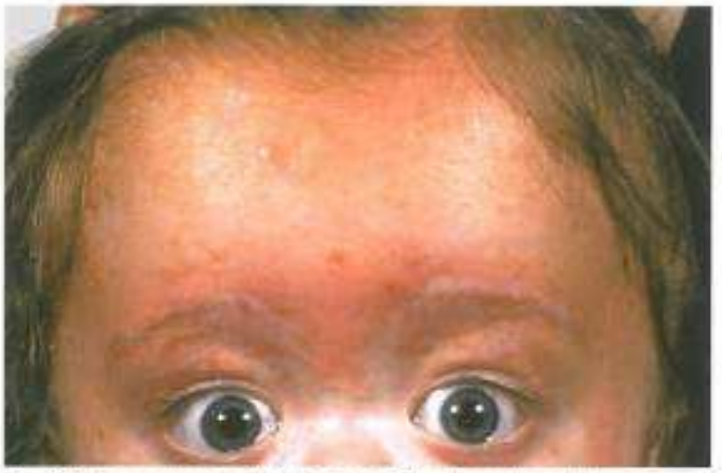


Fig. 22.33 Langerhans' cell histiocytosis. Discrete papules and plaques are visible around the eyebrows and glabella. There is frontal bossing and exophthalmos. Bony lesions, diabetes insipidus, exophthalmos and mucocutaneous lesions are characteristic of Hans–Schüller–Christian disease.

Management

The histology is characteristic. There are large histiocytic cells with a pink cytoplasm with lobulated bean-shaped nuclei in the upper dermis, often forming Pautrier-like microabscesses in the epidermis (Fig. 22.34). Electron microscopy shows rod-shaped (Birkbeck) granules in the cytoplasm. Some are vesicular at their ends, resembling a tennis racquet (Fig. 22.35). Immunostaining for S100, CD45, CD101 and CD1a is positive. Prognosis varies in these conditions and so, therefore, does the treatment. Topical nitrogen mustard is effective for the skin lesions. Vinblastine, imatinib, etoposide, other chemotherapeutic regimens and bone marrow transplantation are used in multisystem disease.

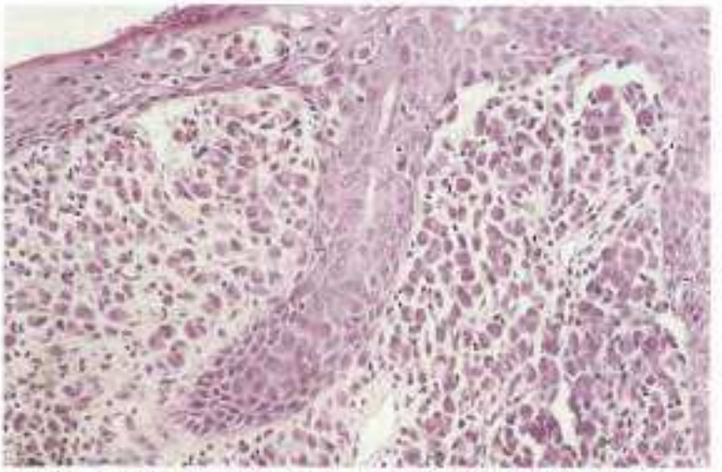


Fig. 22.34 Langerhans' cell histiocytosis. The epidermis and dermis are infiltrated by uniform histiocytes with abundant eosinophilic cytoplasm and irregular vesicular and often reniform nuclei. Occasional eosinophils are present.

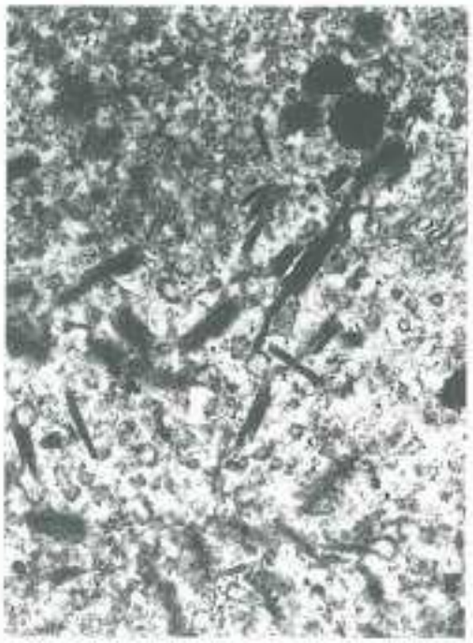


Fig. 22.35 Langerhans' cell histiocytosis. Rod-shaped granules (Birbeck granules) in the cytoplasm are characteristic of Langerhans' cell. Some are vesicular at their ends, resembling a tennis racquet.

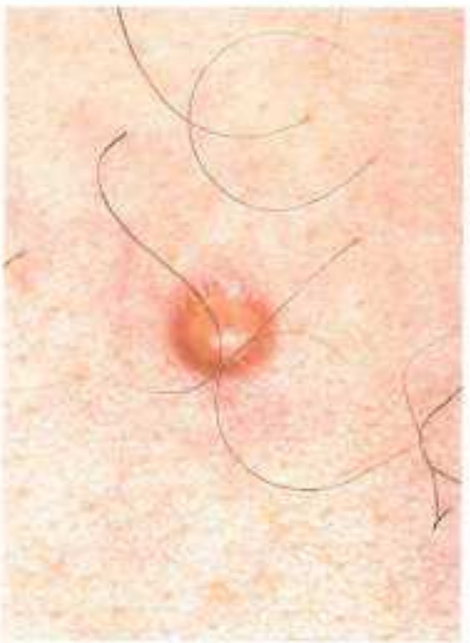


Fig. 22.36 Juvenile xanthogranuloma. A few yellow papules occur, particularly on the head and neck, in early life and subsequently disappear without incident. Very occasionally there is systemic involvement.

TYPE II NON-LANGERHANS' CELL HISTIOCYTOSES

- **Juvenile xanthogranuloma** A benign self-healing cutaneous eruption of infancy and childhood (Fig. 22.36) which is described in Chapter 9.
- **Benign cephalic histiocytosis** Rare, benign and also self-healing. Characteristic comma-shaped bodies consisting of two electron-dense membranes separated by a less dense space are found in the cytoplasm on electron microscopy. It is twice as common in males. There are flat-topped, yellow-brown or flesh-coloured papules, particularly on the upper face (forehead, eyelids and cheeks), which spread to the ears, neck and scalp but also sometimes to the upper part of the body. It resolves within the first year, leaving postinflammatory pigmentation.
- **Generalized eruptive histiocytosis** A very rare but striking form because of the numerous firm red papules on the body without mucous membrane or systemic involvement. It consists of a dense monomorphous histiocytic infiltrate in the upper dermis with a few lymphocytes. It gradually disappears spontaneously and may represent a primitive form of the other forms of non-histiocytoses.
- **Papular xanthoma** An exceedingly rare condition with normolipaemia and characteristic histology, consisting almost entirely of foamy cells and no primitive histiocytic phase.
- **Haemophagocytic lymphohistiocytosis** is a rare life-threatening, rapidly progressing reactive proliferation of histiocytes and uncontrolled phagocytosis induced by T cell activation (possibly secondary to infection) involving the liver, spleen and bone marrow, skin, lymph nodes and central nervous system (CNS). Histologically, there are many lymphocytes and haemophagocytosis is present. It occurs in two forms. One presents in children and is inherited as an autosomal recessive and the other occurs in adults with an underlying disease (HIV, malignancy or connective tissue disease).
- **Malignant histiocytosis** (Type III non-Langerhans' cell histiocytosis) is extremely rare.
- **Rosai–Dorfman disease** may occur in a systemic form with sinus histiocytosis and massive lymphadenopathy, particularly of the cervical nodes where the nodes are expanded by proliferation of large histiocytes, mainly in the sinuses but often with lymphocytes in their cytoplasm. It may occur in any organ including the skin with a raised ESR and polyclonal gammopathy. It is usually benign but occasionally there is general lymphadenopathy, fever, weight loss, malaise and night sweats. It may occur solely in the skin as a solitary (Fig. 22.37) or widespread nodules.
- **Necrobiotic xanthogranuloma** A rare chronic progressive granulomatous disease involving the lymph nodes, liver, spleen, eyes (this is common with scleritis, episcleritis and keratitis potentially leading to blindness), mucosa, myocardium, lung, larynx, pharynx, skeletal muscles, kidney, ovary, intestine and skin. All layers of the latter are involved with large zones of necrobiosis, surrounded by well-formed palisading lymphohistiocytic granulomas, which are not dissimilar from necrobiosis lipoidica. There are indurated yellow plaques and nodules

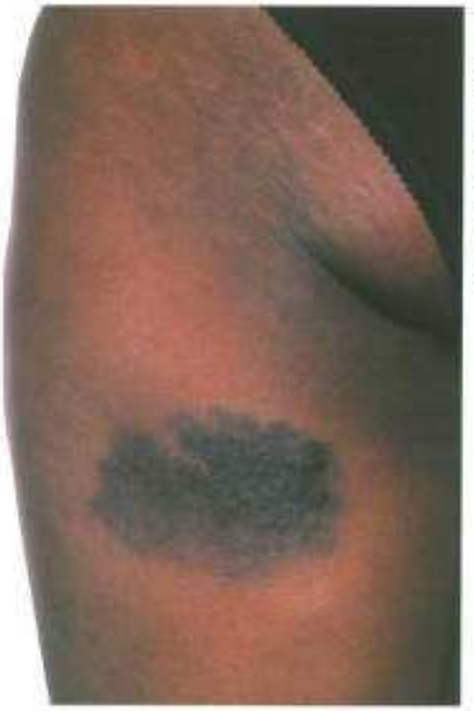


Fig. 22.37 Extranodal Rosai–Dorfman disease. There is a solitary plaque, which would be unlikely to be diagnosed clinically, but the pathology is characteristic and particular emperipolesis (engulfment of lymphocytes by histiocytes) occurs.

with superficial telangiectasia, which may ulcerate and scar. It is of rapid onset. 80% are periorbital (Fig. 22.38), but the trunk and extremities may be involved. It is associated with lymphoproliferative and haematological disorders. 80% have a monoclonal gammopathy (usually IgG). 10% proceed to myeloma. The cutaneous lesions may appear before the blood. Four types have been proposed:

1. adult onset xanthogranuloma without systemic involvement
2. adult onset xanthogranuloma with systemic disease (e.g. Erdheim–Chester disease)
3. necrobiotic xanthogranuloma
4. xanthogranuloma with asthma.

Steroids, chlorambucil and autologous peripheral stem cell transplantation are regular therapies.

- **Erdheim–Chester disease** A rare non-LC histiocytosis involving multiple organs, principally, in descending order of frequency, bone, brain, eyes, kidney, aorta, lungs and heart (cardiomyopathy). There is osteosclerosis of the distal femur, proximal tibia and fibula. The skin lesions consist of scattered yellow-red papules and nodules, which are S100-negative, CD1a-negative, but CD68-positive. It is rapidly progressive with a significant mortality.
- **Sea-blue histiocyte syndrome** A rare inherited disorder characterized by histiocytes with deep azure-blue cytoplasmic granules involving the bone marrow, lymph nodes, spleen, liver, lungs, CNS, eyes and skin (brown pigmentation with facial nodules). It is associated with chronic myeloid leukaemia and light chain disease.

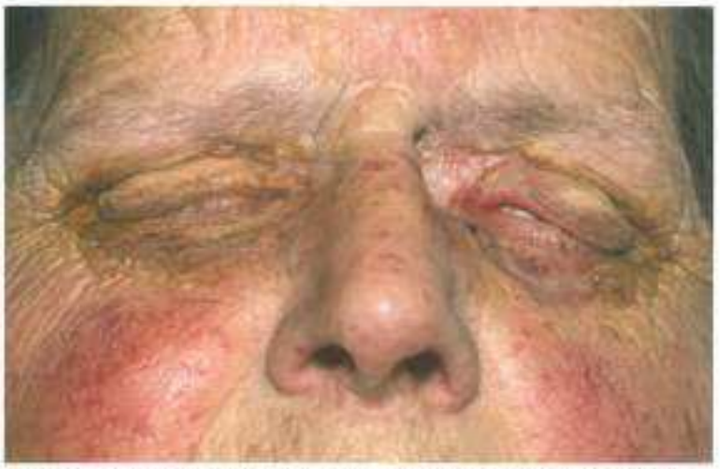


Fig. 22.38 Necrobiotic xanthogranuloma. There are xanthomatous plaques and nodules especially around the eyes, telangiectasia, involvement of the reticuloendothelial system and a monoclonal gammopathy. (Courtesy of Prof. Edward Wilson Jones.)

MULTICENTRIC RETICULOHISTIOCYTOSIS

A rare granulomatous phagocytic histiocyte reaction to an unknown, but sometimes paraneoplastic stimulus, that affects the skin, mucosae and synovia and causes a destructive arthritis.

Aetiology

It is more common in middle-aged females. Approximately 20% are associated with malignant disease, particularly carcinoma of the colon, breast, bronchus, cervix, ovary or stomach, or with autoimmune disease, including Sjögren's syndrome, diabetes mellitus and thyroid disease. There is a distinctive histology of a granulomatous proliferation of histiocytes, many of which are multinucleate and laden with lipids.

Clinical Features

Symptoms

The patient usually presents with either cutaneous or joint symptoms.

Morphology

Initially, there may be a prodrome of a diffuse erythema (Fig. 22.39) that is rather similar to that of dermatomyositis, followed by non-tender, red-brown, firm papules (Fig. 22.40) or nodules.

Distribution

It occurs on the extensor surfaces of the joints (Fig. 22.41) around the nails and on the face, especially nostrils and ears (Fig. 22.42). Other areas may be involved, including mucosae (lips, mouth, tongue and in the nose).

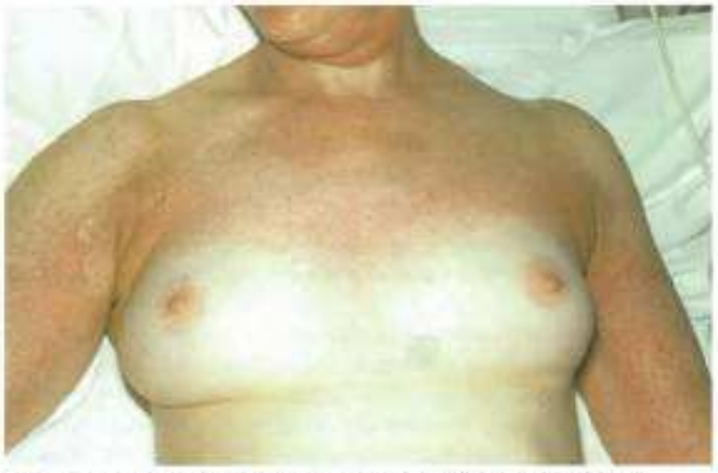


Fig. 22.39 Multicentric reticulohistiocytosis. A diffuse photodistributed erythema simulating dermatomyositis occurs with a destructive arthritis. The pathology is specific. (Courtesy of St Mary's Hospital, London).

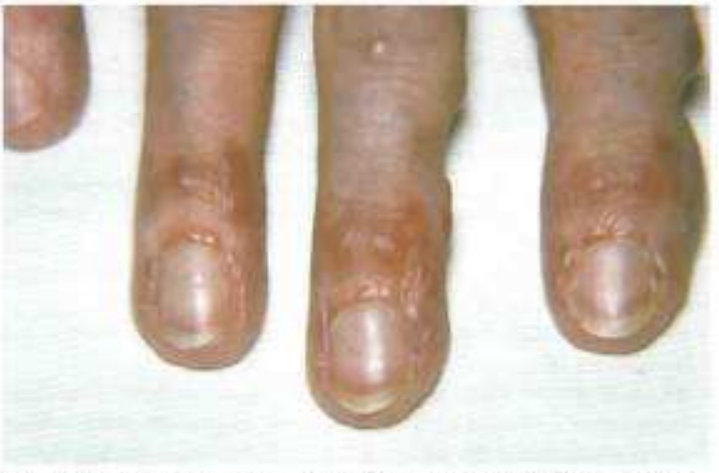


Fig. 22.40 Multicentric reticulohistiocytosis. There are red-brown papules on the fingers and coral bead-like lesions around the nails, which may lead to nail dystrophy, and a destructive arthritis. (Courtesy of St Mary's Hospital, London.)

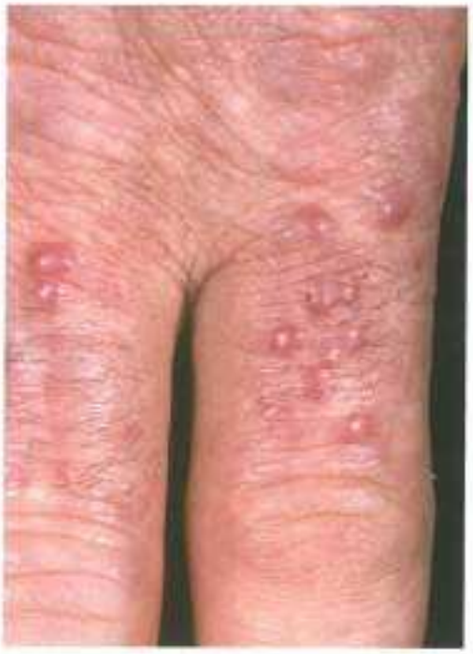


Fig. 22.41 Multicentric reticulohistiocytosis. The red-brown papules occur over extensor surfaces. Some are associated with malignancy and others with autoimmune disease.

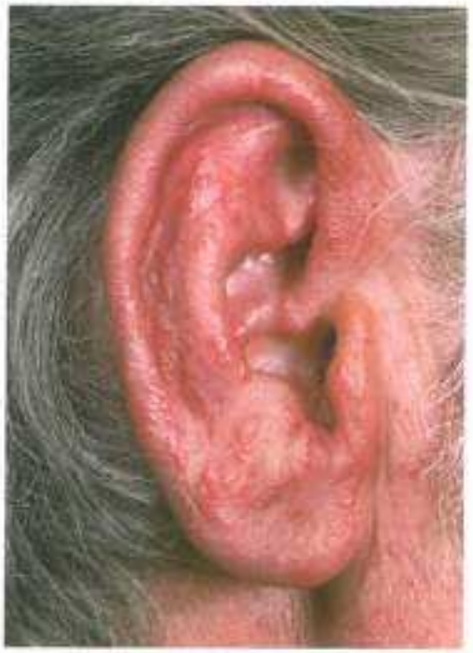


Fig. 22.42 Multicentric reticulohistiocytosis. The papules are non-tender and have a remarkable red-brown colour and a predilection for the ears.

Systemic signs

The arthritis is symmetrical, destructive and mutilating, affecting the interphalangeal joints, knees, wrists, hips, ankles, shoulders, feet and elsewhere. It eventually burns out.

Management

The clinical picture is fairly characteristic but histology confirms the diagnosis. The dermis contains numerous peculiar large mono- and multinucleated giant cells and large periodic acid Schiff (PAS)-positive, lipid-containing histiocytes with a ground-glass cytoplasm (Fig. 22.43). The arthritis is seronegative. Anaemia, raised erythrocyte sedimentation rates (ESR), leucocytosis, eosinophilia and occasionally hypergammaglobulinaemia may occur. There is no specific treatment once malignancy has been ruled out, although systemic steroids and cyclophosphamide have been used. It may remit after many years.

XANTHOMA DISSEMINATUM

A rare nonolipaemic histioxanthomatosis associated with xanthomatous deposits in the skin (Fig. 22.44), eyes, mucosae and meninges and diabetes insipidus.

Aetiology

The cause is unknown. It commences in childhood or early adult life. There is a proliferation of histiocytic cells with lipid deposition as a secondary event. There is a dermal infiltrate of spindle-shaped mononuclear cells, foamy histiocytes, giant cells, polymorphs and eosinophils. The cells have irregularly scalloped borders with extensive cytoplasm and ovoid vesicular nuclei. Ultrastructurally, the changes simulate those seen in juvenile xanthogranuloma and papular xanthomas, but they do not have a primitive histiocytic or inflammatory phase. Cells label with factor XIIIa and kallikrein-protease inhibitor. S100 and CD1a stains are negative but CD68 is positive.

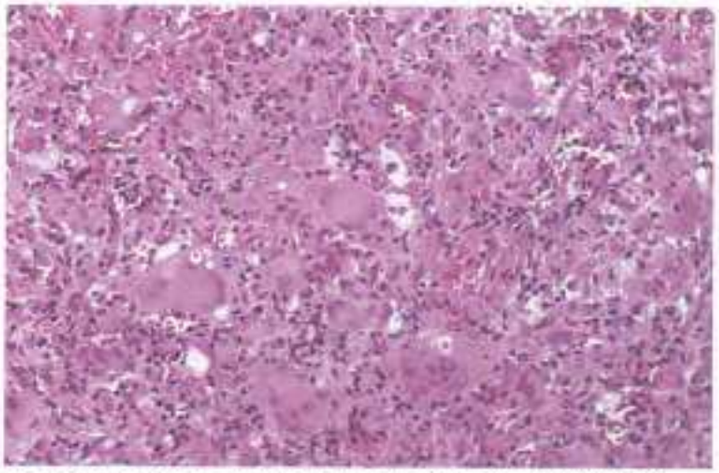


Fig. 22.43 Multicentric reticulohistiocytosis. Note the presence of typical ground glass giant cells.

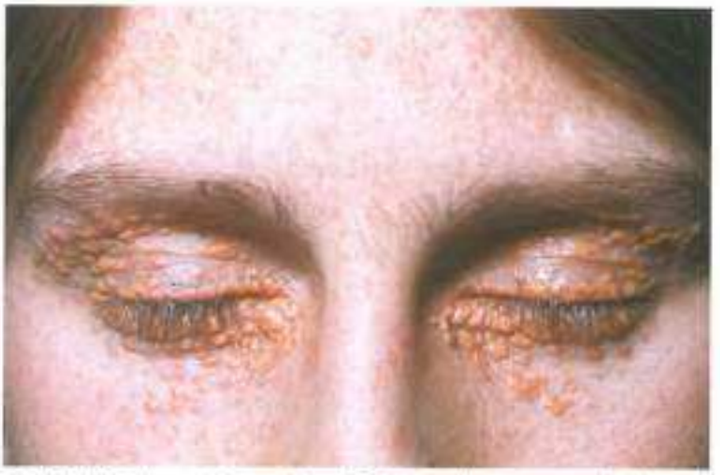


Fig. 22.44 Xanthoma disseminatum. Eruptive xanthoma may occur in the absence of hyperlipidaemia especially around the eyes. (Courtesy of St Mary's Hospital, London.)

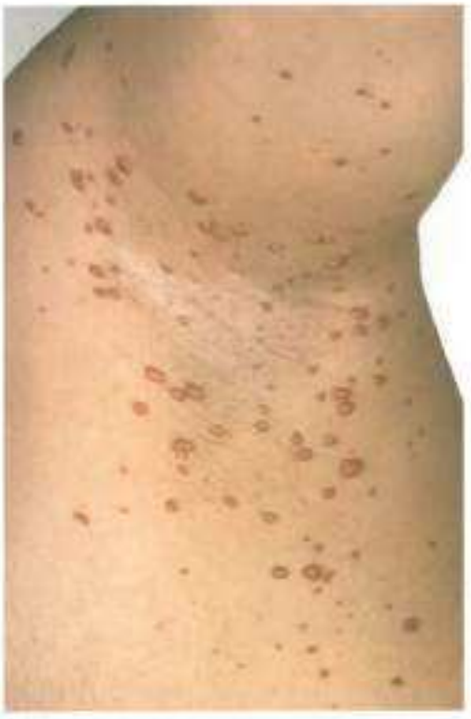


Fig. 22.45 Xanthoma disseminatum. The patient is often covered in yellow-brown papules. Lipid profiles are normal.

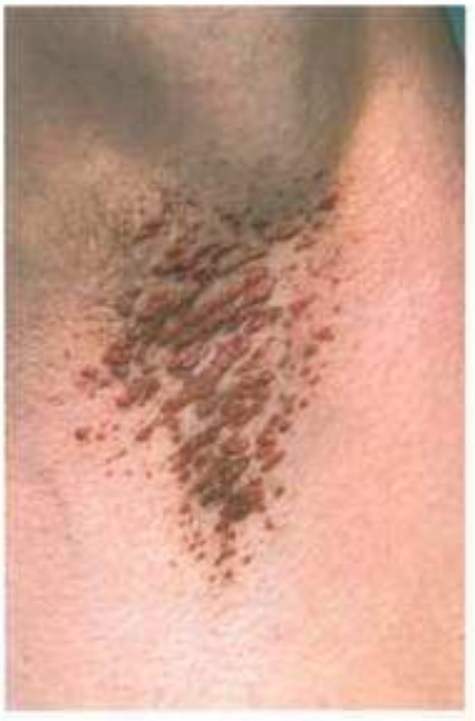


Fig. 22.46 Xanthoma disseminatum. The yellow-brown papules may merge into plaques. It is a systemic disorder giving rise to meningeal, pituitary (particularly manifested by diabetes insipidus), liver and bone marrow involvement.

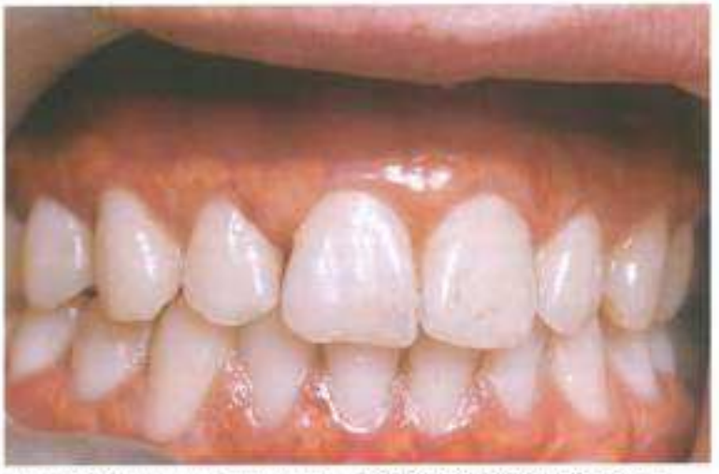


Fig. 22.47 Xanthoma disseminatum. Involvement of the gums, larynx and bronchi is characteristic of this rare histiocytic proliferative disorder. (Courtesy of St Mary's Hospital, London.)

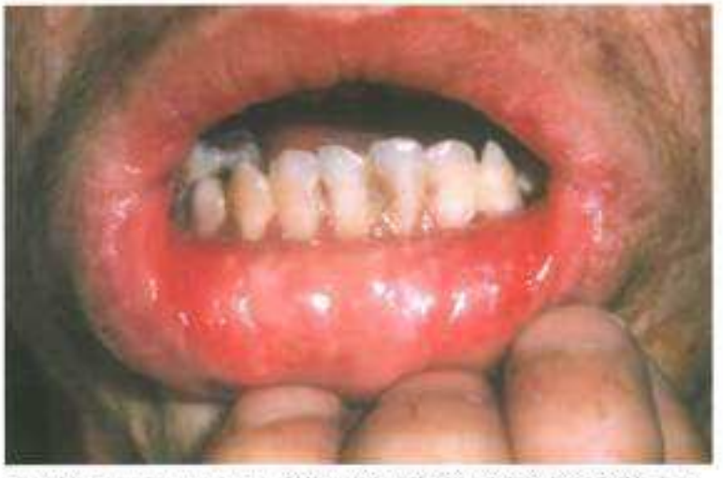


Fig. 22.48 Lipoid proteinosis. Yellow, waxy infiltrations of the lips, eyelids, face and elsewhere occur from deposits of an amorphous hyaline material around blood vessels. It presents after birth with hoarseness and inability to cry.

Clinical Features

Symptoms

Disfiguring skin lesions, particularly around the eyes.

Morphology

There are hundreds of red-brown papules (Fig. 22.45), which become yellowish and subsequently merge into plaques, which are often verrucous.

Distribution

Symmetrical anywhere on the skin but particularly around the eyes, and in clusters in the flexures (Fig. 22.46).

Systemic signs

The mucosae are typically involved, particularly the mouth, gums (Fig. 22.47), larynx, trachea and bronchi, giving rise to hoarseness and airway obstruction. Fleshy orange papules occur in the sclera and cornea. The meninges, pituitary, liver and bone marrow may be affected. Diabetes insipidus, seizures and growth retardation may occur.

Management

The clinical picture is distinctive. Diabetes insipidus does not occur in juvenile xanthogranuloma or papular xanthoma. A skin biopsy will establish the diagnosis. The patients have normal lipid profiles. When the meninges are involved, the condition is analogous to Hand–Schüller–Christian disease. Diabetes insipidus, which is present in 50%, is vasopressin sensitive but otherwise there is no specific treatment.

Other infiltrative disorders which may involve the eyelids and mucous membrane such as amyloid or *lipoid proteinosis* (Fig. 22.48) have different clinical presentations. In particular in lipoid proteinosis infiltration of the laryngeal mucosa gives rise to a hoarse cry at birth and hoarseness thereafter. It is a very rare autosomal recessive disorder due to mutations in the ECM1 (extracellular matrix protein 1) gene.

Xanthomatoses

These conditions are caused by hyperlipidaemia secondary either to a primary genetic defect or to abnormal metabolism. Lipid is deposited in the skin and elsewhere.

Aetiology

Pathologically, xanthomas consist of foam cells, which are tissue macrophages that have phagocytosed the lipid part of lipoproteins. Lipids are insoluble but are transported in soluble form in the plasma as lipoproteins, which can be separated out by electrophoresis or by ultracentrifugation into five fractions (chylomicrons; pre-β- or very low density lipoproteins (VLDL); intermediate density lipoproteins; β- or low density lipoproteins (LDL); and high density lipoproteins (HDL)). Chylomicrons are the largest and scatter transmitted light, causing the plasma to appear milky when they are present in excess. They consist of 85% triglycerides and are induced by a fat-rich diet. LDL are the smallest and consist of 50% cholesterol. VLDL are 50% triglycerides and 30% cholesterol, and intermediate density lipoproteins are 50% triglycerides and 50% cholesterol.

Exogenous dietary fat is incorporated by intestinal cells into the chylomicrons, which enter the lymphatics and bloodstream to be transported to the peripheral capillaries in adipose and muscle tissue. Apolipoprotein C-II (APOC-II) on chylomicrons activates lipoprotein lipases, which hydrolyse the triglyceride fraction of chylomicrons into fatty acids and monoglycerides; these are taken up by fat and muscle cells to resynthesize triglycerides intracellularly. The remaining lipoprotein particles, called chylomicron remnants, return to the circulation and are removed by receptors in the liver.

The endogenous pathway transports newly synthesized or recycled triglycerides and cholesterol all the time and is responsible for most of the lipoproteins in plasma. VLDL are secreted into plasma by the liver and travel to the fat and muscle where the triglycerides are hydrolysed by lipoprotein lipase. The VLDL remnants (known as intermediate density lipoproteins) then either enter the circulation and are removed by the liver or are converted to LDL and the remainder of the triglycerides is lost. LDL then delivers cholesterol to the cells.

The primary hyperlipidaemias are not common but are important because they are associated with arteriosclerosis, pancreatitis and diabetes. Hyperlipidaemias may also occur secondary to:

- Hepatic disorders – haemochromatosis, congenital atresia or hypotresia of the bile ducts
- Renal disease – nephrotic syndrome
- Haematological disorders – myeloma
- Pancreatic disorders – chronic pancreatitis
- Hormonal disorders – diabetes mellitus, myxoedema
- Drugs – thiazides, beta-blockers, epanutin, ciclosporin, retinoids, oestrogens, alcohol, olanzaprine and ritonavir.

Clinical Features

The lipids are deposited in a variety of ways:

- **Xanthelasmas** flat yellow plaques (Fig. 22.49) around the eyes
- **Xanthomas** yellow papules (Fig. 22.50) or nodules
- **Xanthoma eruptiva** a myriad of yellow papules (Fig. 22.51) that erupt over the buttocks, thighs, arms, forearms, back and chest

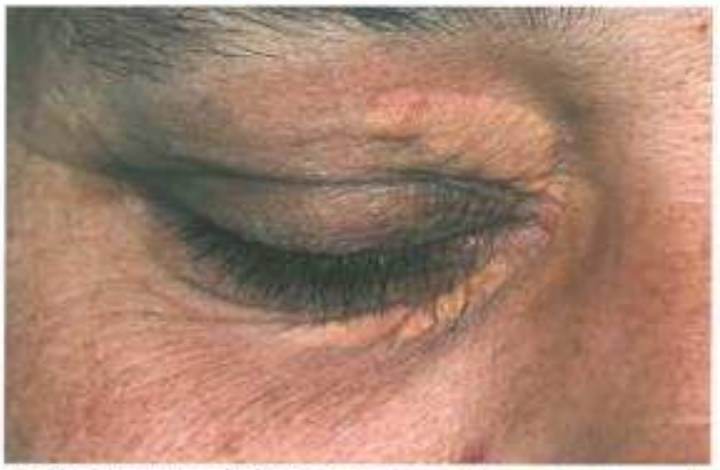


Fig. 22.49 Xanthelasma. Flat yellow plaques around the eyes are common and the patients are usually normolipidaemic.

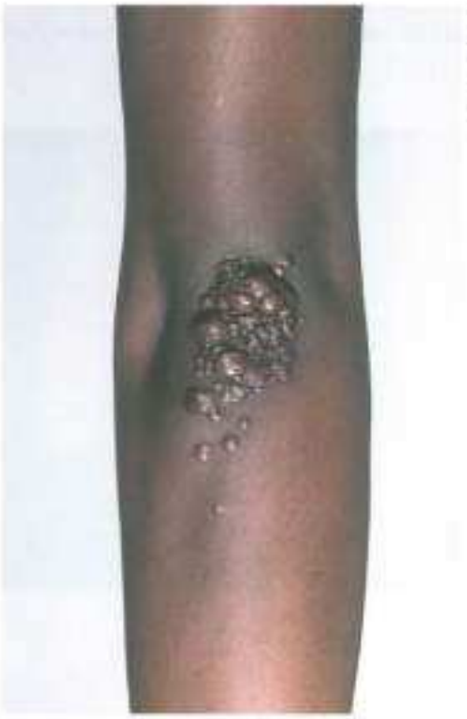


Fig. 22.50 Xanthomas. Yellow nodules occur particularly over bony prominences, as in this West Indian woman.

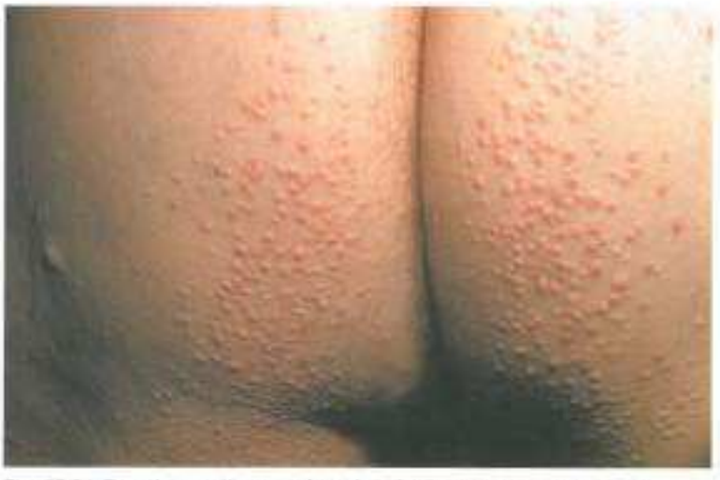


Fig. 22.51 Eruptive xanthomas. A myriad of yellow papules appear quite suddenly and extensively, including over the buttocks.

- **Xanthoma planum** in the creases (Fig. 22.52) of the palms.
- **Xanthoma tendinosum** lobulated nodules over the elbows and knees (Figs 22.53 and 22.54), or along the course of tendons, particularly the Achilles and over the backs of the hands.

Eruptive xanthomas are usually associated with chylomicron excess, secondary to uncontrolled diabetes mellitus (Fig. 22.55), alcohol abuse or exogenous oestrogens. This is caused by reduced lipoprotein lipase activity or increased hepatic VLDL, which results in the chylomicrons being less able to compete with VLDL for lipoprotein lipases. The xanthoma may erupt in primary hyperlipidaemias, particularly lipoprotein lipase deficiency in children (type I hyperlipidaemia) and in type V familial adult type hyperlipidaemia. Atheroma is not associated with either of these two types. The eruptive xanthomas may be quite inflammatory and often pruritic and tender and have an erythematous halo around them. The Koebner phenomenon sometimes occurs.

Tuberoeruptive and tuberous xanthomas mostly occur in type III hyperlipidaemia. There are increased VLDL remnants and chylomicron remnants, which result in raised cholesterol and triglyceride levels and there is a distinct risk of atherosclerosis.

Tendon xanthomas occur particularly in *heterozygous familial hypercholesterolaemia*, where the LDL and cholesterol are raised, rather than in the homozygous form since patients with the latter succumb before xanthomas develop. They also occur in *cerebrotendinous xanthomatosis*, a disorder of bile acid metabolism resulting in an accumulation of cholesterol and formation of atheroma.

Plane xanthomas may occur in various sites. Intertriginous plane xanthomas (finger webs, axillae and antecubital and popliteal fossae) are pathognomonic for homozygous familial hypercholesterolaemia. In the palmar creases, they are virtually diagnostic of type III familial dysbetalipoproteinaemia.

Around the eyes, xanthelasma may or may not be caused by hyperlipidaemia.

Plane and other xanthomas also occur in disorders of cholestasis (Fig. 22.56), particularly primary biliary cirrhosis or biliary atresia (Fig. 22.57). The patients are unable to excrete cholesterol into bile; consequently, it accumulates in plasma and binds with albumin and phospholipids (known as lipoprotein X). The cholesterol level is often in excess of 500 mg/dl.

There is a diffuse symmetrical normolipaemic form of plane xanthoma (Figs 22.58 and 22.59) that occurs particularly on the face, trunk and sides of the neck. Causes include dysglobulinaemia, paraproteinaemia, multiple myeloma, monoclonal gammopathy, cryoglobulinaemia, leukaemia, lymphoma or rheumatoid arthritis.

In general, those patients with a raised triglyceride-rich chylomicron level suffer from pancreatitis and those with raised cholesterol-rich LDL, VLDL or VLDL remnants develop atherosclerosis. Hyperlipidaemias can be divided into groups (Fredrickson's types).

- **Type I hyperlipoproteinaemia** An autosomal recessive deficiency of lipoprotein lipase (necessary for hydrolysing triglycerides to free fatty acids and glycerol) that results in the accumulation of chylomicrons and thus triglycerides. Eruptive xanthomas occur and the serum is lipaemic. Abdominal pain, hepatosplenomegaly and pancreatitis are usual. An increase in chylomicrons can be induced by diets that are rich in fat, and the condition responds to restriction of dietary fat. There is no risk of coronary artery disease.
- **Type II hypercholesterolaemia** An autosomal dominant lack of LDL receptors result in the accumulation of LDL and very high cholesterol levels (type IIa). In African-Americans, there is an accelerated degradation of the LDL receptor secondary to a PCSK9 (proprotein convertase subtilisin/kexin 9) mutation. Occasionally triglycerides are also raised (type IIb). Heterozygotes develop cardiovascular disease and intertriginous plane xanthomas, xanthelasmas, tuberous and tendon xanthomas and a premature corneal arcus.

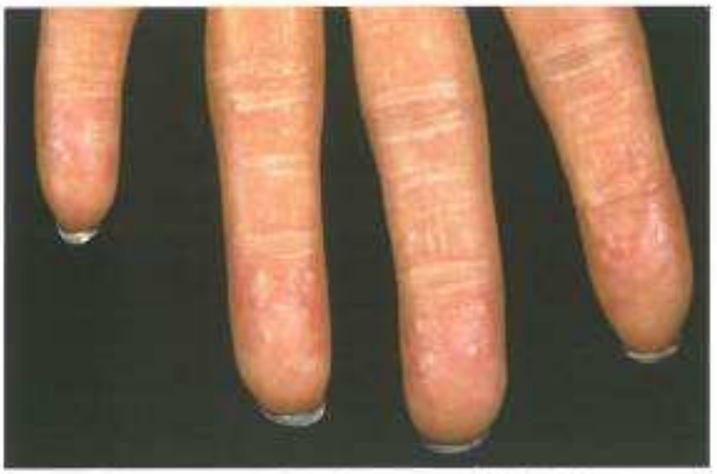
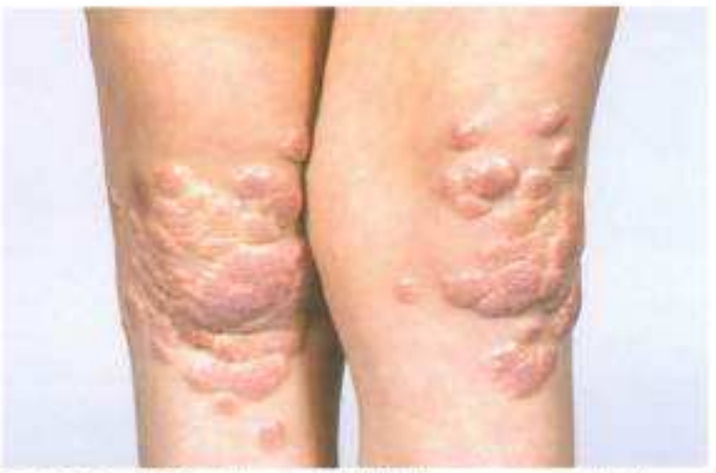
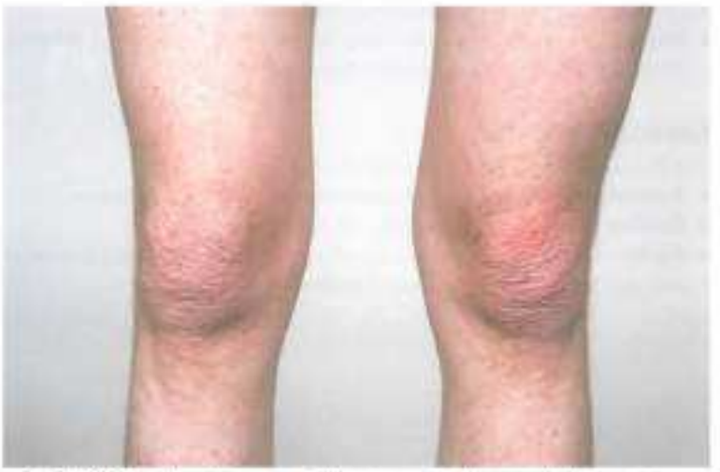


Fig. 22.52 Plane xanthomas. The palmar creases are filled with plane xanthomas. This occurs in type III hyperlipidaemia and, as in this patient, in primary biliary cirrhosis.





Figs 22.53 and 22.54 Xanthomas. Lobulated tumours occur over the elbows and knees (Fig. 22.53) or along the course of tendons, when they may be known as xanthoma tendinosum. This child had Alagille syndrome (biliary hypoplasia) successfully treated with a liver transplant (Fig. 22.54).

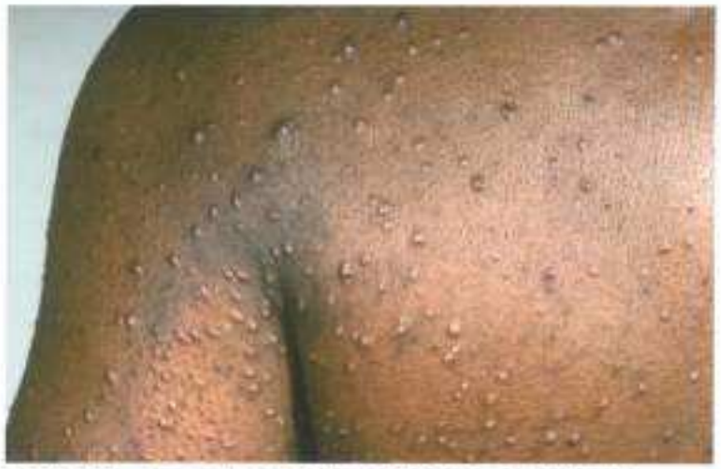


Fig. 22.55 Eruptive xanthomas. This man's diabetes was out of control. Other causes are alcohol abuse, exogenous oestrogens and types I and V hyperlipidaemias.

- **Type III hyperlipidaemia** In familial dysbetalipoproteinaemia, APOE2 is present on the lipoproteins rather than APOE3 and APOE4, which bind hepatic receptors and facilitate the clearance of chylomicron remnants and VLDL remnants from the plasma. Consequently chylomicron and VLDL remnants increase and there is hypercholesterolaemia and hypertriglyceridaemia. Homozygous APOE2 states are common but familial dysbetalipoproteinaemia is not and the gene requires an additional abnormality of VLDL overproduction such as occurs in diabetes mellitus, hypothyroidism or obesity. Premature atherosclerosis results. Tuberous and tuberoeruptive xanthomas occur and palmar plane xanthomas are a striking feature.
- **Type IV hyperlipidaemia** There is often excessive carbohydrate ingestion and alcohol abuse, which increases VLDL synthesis in the liver of normal individuals and those with type IV disease. The patients are obese and have glucose intolerance and hyperinsulinaemia. The serum may be turbid. Eruptive and palmar xanthomas occur. Cardiovascular disease and pancreatitis are common.
- **Type V hyperlipidaemia** There are elevated levels of chylomicrons and VLDL. Diabetes mellitus, hyperuricaemia and eruptive xanthomas result. Lipaemia, abdominal pain, hepatosplenomegaly and pancreatitis occur as in type I disease. Hypertension and polyneuropathy may occur.

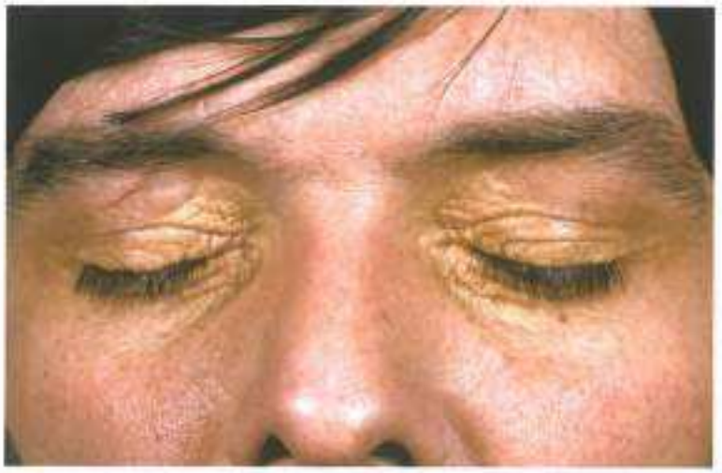


Fig. 22.56 Xanthelasmas. Plane xanthomas may develop in disorders of cholestasis. This patient is jaundiced.

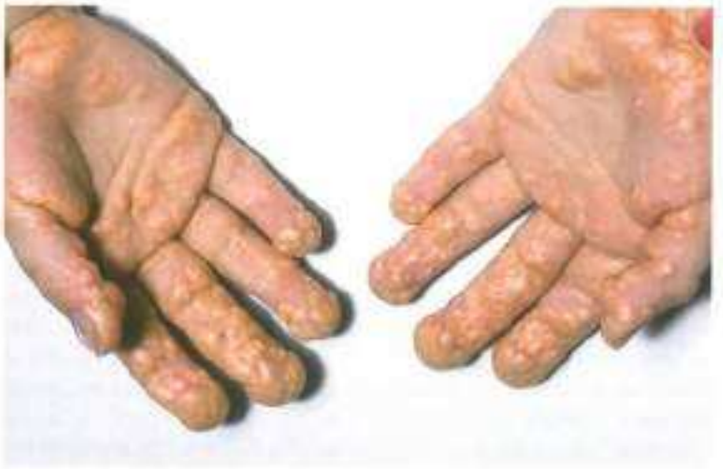


Fig. 22.57 Biliary hypoplasia. These tuberous xanthomas are very characteristic of Alagille syndrome.

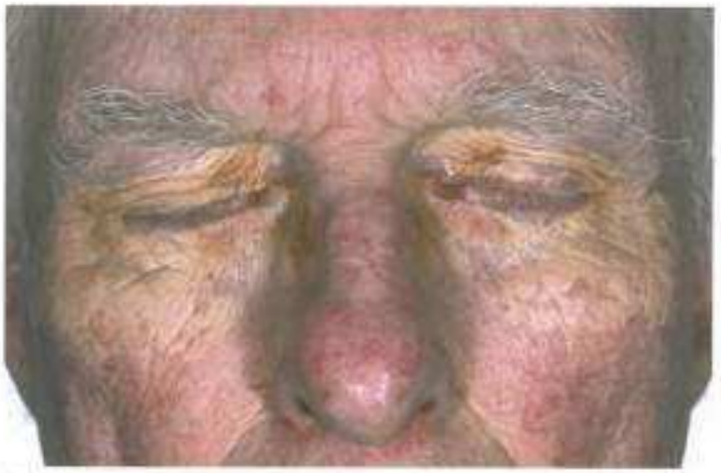


Fig. 22.58 Diffuse plane xanthomatosis. This patient was normolipaemic. The xanthomas were secondary to multiple myeloma.

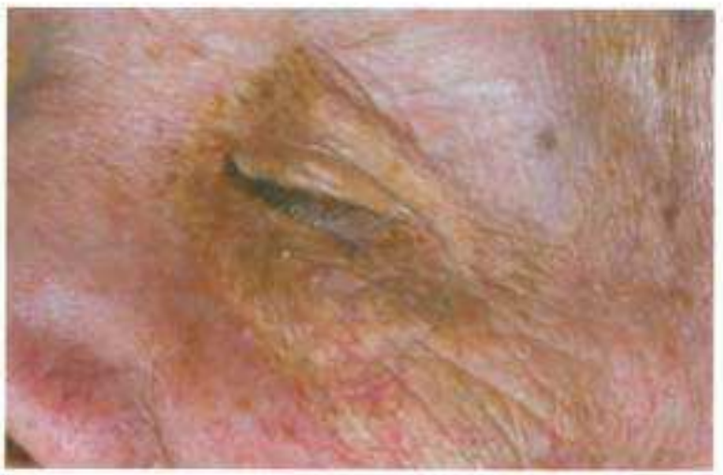


Fig. 22.59 Diffuse plane xanthomatosis. The plaques around the eyes are much more diffuse than xanthelasma.

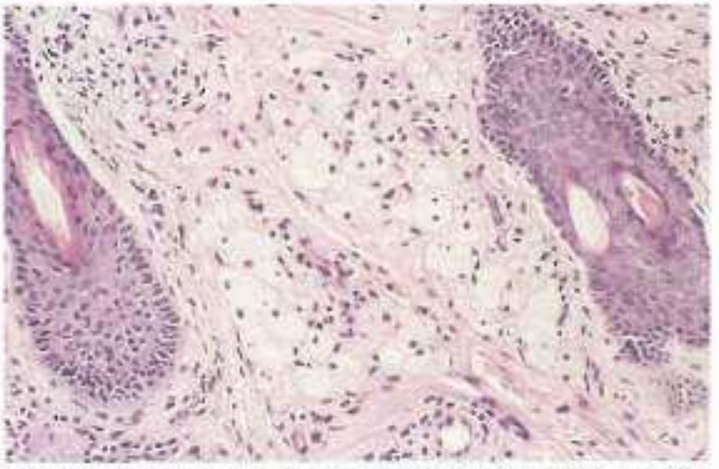


Fig. 22.60 Xanthoma. The xanthoma cells are very regular, have uniformly foamy cytoplasm and small hyperchromatic nuclei.

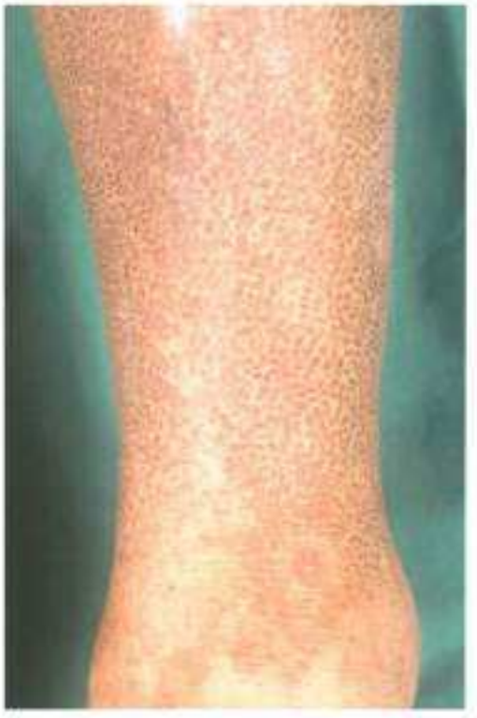


Fig. 22.61 Lichen amyloid. Brown discrete papules are present, producing a rippled effect. It is more common in patients from the Indian subcontinent, South America and the Orient.

Management of hyperlipidaemia

The management of these diseases is complicated but involves the use of lipid-lowering agents and the help of a dietitian. The diagnosis may be made by lipoprotein electrophoresis. The histology is of an infiltrate of xanthoma cells (Fig. 22.60).

Amyloidosis

Amyloidosis is characterized by the extracellular deposition of protein, which leads to changes in tissue architecture and function. Amyloid is an eosinophilic amorphous hyaline substance, as seen with haematoxylin and eosin stain, and has a high affinity for Congo red and other stains. Under polarized light, there is an apple-green birefringence. Ultrastructurally, it is composed of linear, non-branching, tubular fibrils of 7.5–10 nm in width; these are loosely arranged in a network. The fibrils are composed of several filaments that are arranged in a β-pleated sheet configuration and not in the usual α-helical form. This cross-linked pattern of β-sheets can be seen with X-ray diffraction. Amyloid may be deposited primarily in the skin with no evidence of it elsewhere or as a secondary phenomenon associated with visceral deposition, particularly in the heart, kidneys, liver and gastrointestinal tract. In vivo scintigraphy using human serum amyloid P component labelled with iodine-123 is helpful to delineate the extent of systemic amyloid and its response to treatment. Amyloid can be seen most easily in frozen sections rather than in formalin-processed material. Amyloid is also an incidental finding in various skin tumours, including intradermal naevi and basal cell carcinoma, but has no clinical significance.

Amyloidoses may be classified as:

Primary cutaneous

- Lichen amyloidosis, macular amyloid and nodular amyloid

Systemic amyloid

- Primary (caused by occult plasma cell dyscrasia or myeloma)
- Secondary to chronic inflammation (e.g. rheumatoid arthritis) or infection (e.g. tuberculosis)
- Heredofamilial syndromes (e.g. Familial Mediterranean fever)
- Haemodialysis related.

Primary and myeloma-associated systemic amyloidosis have immunoglobulin light chains known as amyloid L (AL) as precursors to the amyloid fibril protein. These are usually the lamda type of light chain, coming from the serum immunoglobulins of the plasma cell dyscrasia.

In the secondary forms, the serum precursor protein (serum amyloid A) is a high density lipoprotein and acute phase reactant in health, which probably stimulates macrophages to form amyloid A (AA) protein and may be the result of chronic elevation of serum AL in chronic disease.

AA is the amyloid fibril protein involved in familial Mediterranean fever and the Muckle–Wells syndrome (Ch. 18).

The familial amyloid polyneuropathies do not affect primarily the skin. The amyloid protein involved is prealbumin (transthyretin).

Amyloidosis associated with haemodialysis affects articular structures and is the result of deposition of β_2-microglobulin, which accumulates because it is not being cleared by the dialysis membrane. Nearly every patient develops it. Carpal tunnel syndrome is common. Cutaneous manifestations are rare but do include wrinkling of the fingers and lichenoid truncal lesions.

PRIMARY AMYLOIDOSIS

The deposition of amyloid in the skin only.

Aetiology

The causes of lichen and macular amyloid are unknown. They are more common in the Middle East, Asia, China and Central and South America. They may be sporadic or familial. The deposits of amyloid are found in the papillary dermis and may displace the dermal papillae laterally. This close apposition to the epidermis has suggested that friction may be the cause, particularly because similar changes may be seen in lichen simplex, prurigo and notalgia paraesthetica. It is probable that degenerate keratin and necrotic epidermal cells are transformed into amyloid by dermal macrophages and fibroblasts.

Nodular amyloid is the rarest, occurs in older Caucasians, especially females, and is thought to be a cutaneous plasmacytoma that produces immunoglobulin light chains as a precursor to the AL-type fibril proteins seen in myeloma-associated systemic amyloid. The amyloid is deposited deep in the dermis or subcutis. It is occasionally associated with systemic amyloid.

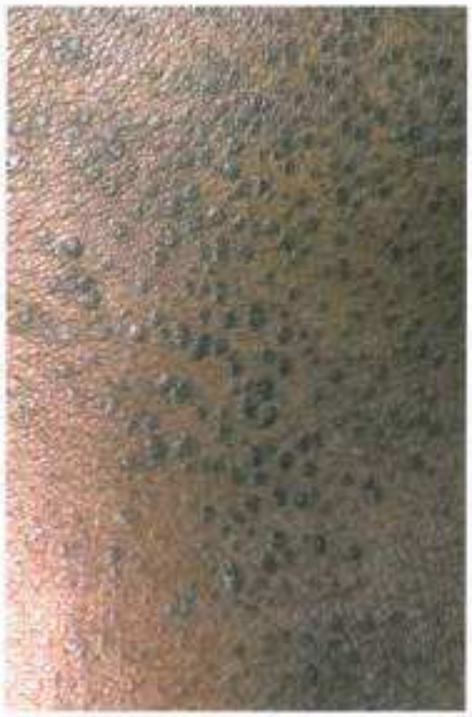


Fig. 22.62 Lichen amyloid. There are discrete, hyperpigmented papules. Biopsy is necessary for diagnosis.

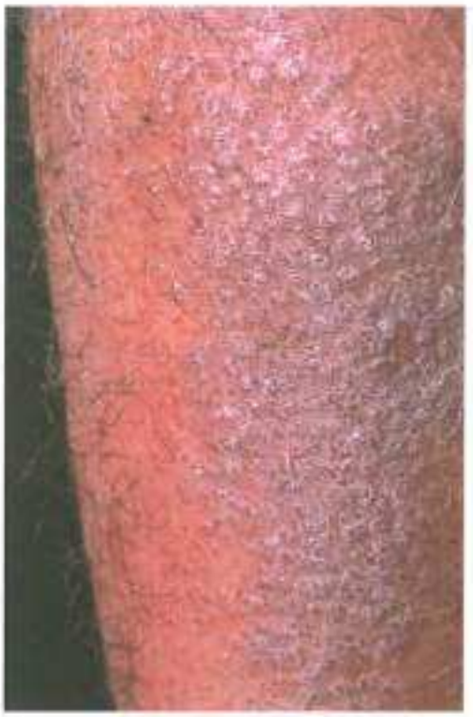


Fig. 22.63 Lichen amyloid. The fronts of the shins are affected. The papules must be distinguished from those of lichen simplex.

LICHEN AMYLOID

Clinical Features

Symptoms

The condition is chronic and very itchy.

Morphology

A papular eruption (Fig. 22.61) occurs that may coalesce into thickened plaques simulating lichen simplex (Figs 22.62 and 22.63) or even hypertrophic lichen planus.

Distribution

The shins most frequently but also the thighs and upper limbs.

MACULAR AMYLOID

Clinical Features

Symptoms

Moderate irritation.

Morphology

Very small, pigmented macules that coalesce to form a characteristic reticulate or 'rippled' pattern (Fig. 22.64). Papular forms do develop.

Distribution

The interscapular area especially (Fig. 22.65) but the back generally is involved; the chest and the extensor aspects of the extremities are also affected.

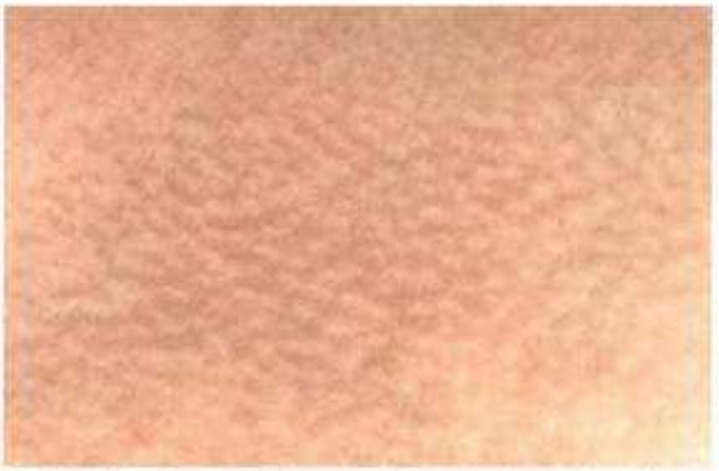


Fig. 22.64 Macular amyloid. Very small, pigmented macules coalesce to form a rather characteristic rippled pattern.

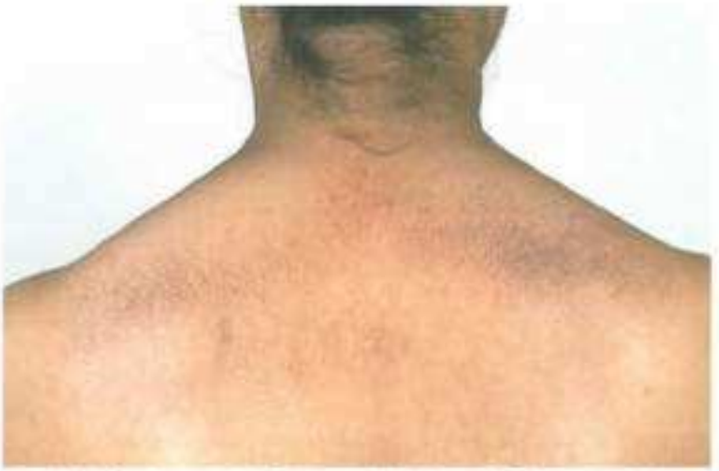


Fig. 22.65 Macular amyloid. The upper back is involved. Pigmentation is the striking feature. It is not uncommon in Indian races.

NODULAR OR PLAQUE AMYLOID

Clinical Features

Symptoms

Asymptomatic.

Morphology

Brown-pink, waxy plaques (Fig. 22.66) or nodules occur, often with overlying atrophy and petechial haemorrhages, which can be quite large and subcutaneous or can be superficial plaques.

Distribution

The plaques occur singly or in multiples on the limbs, trunk, genitalia and face. Usually confined to the skin but systemic amyloidosis may occur.

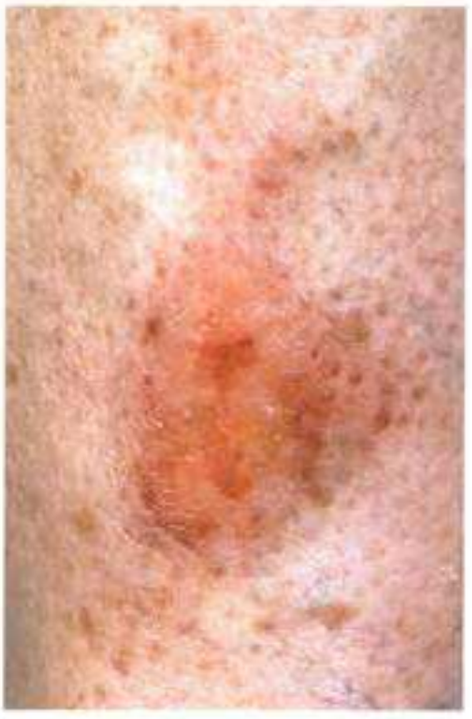


Fig. 22.66 Plaque amyloid. The skin is atrophic and purpura occurs within the lesion. This lesion was on the shin. (Courtesy of Dr Michèle Clement.)

Management

The diagnosis may be made by skin biopsy and stains for amyloid. Treatment is not very satisfactory. Topical steroids may help initially, particularly under occlusion. Some cases of lichen amyloid have benefited from dermabrasion. Early stages of nodular amyloid may be excised.

SYSTEMIC AMYLOIDOSIS

A rare disorder of protein metabolism that results in extracellular deposition of amyloid in mucocutaneous structures and certain viscera, which includes the heart, kidneys, liver and gastrointestinal tract but never the brain. Carpal tunnel syndrome and macroglossia are common.

Aetiology

Systemic amyloidosis most often results from an underlying plasma cell abnormality, including myeloma. It is most common in elderly males. In myeloma-associated amyloidosis, the deposits of amyloid in the skin are found in the papillary dermis and account for the papules that are seen clinically; if amyloid is also deposited in the deep reticular dermis, nodules and plaques may occur. The infiltration of blood vessel walls then leads to the additional clinical finding of purpura. Amyloidosis secondary to chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease and osteomyelitis, rarely produces cutaneous abnormalities but principally involves the kidneys, spleen, alimentary tract and adrenals. The most common presentation is that of the nephrotic syndrome.

Clinical Features

Symptoms

Non-specific ill health, carpal tunnel syndrome, macroglossia and skin lesions, including eyelid purpura precipitated by straining at stool or coughing.

Morphology

Petechiae, purpura and ecchymoses (Fig. 22.67) occur either spontaneously or after minimal trauma. In addition there are smooth, waxy, often haemorrhagic papules, plaques or sometimes nodules.

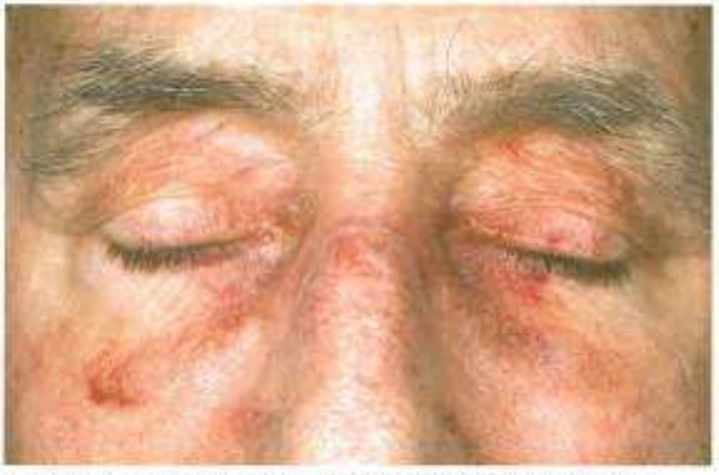


Fig. 22.67 Systemic amyloidosis. Bleeding into the skin (purpura) due to infiltration of the blood vessel walls by amyloid around the eyes is common, precipitated by straining at stool or coughing.

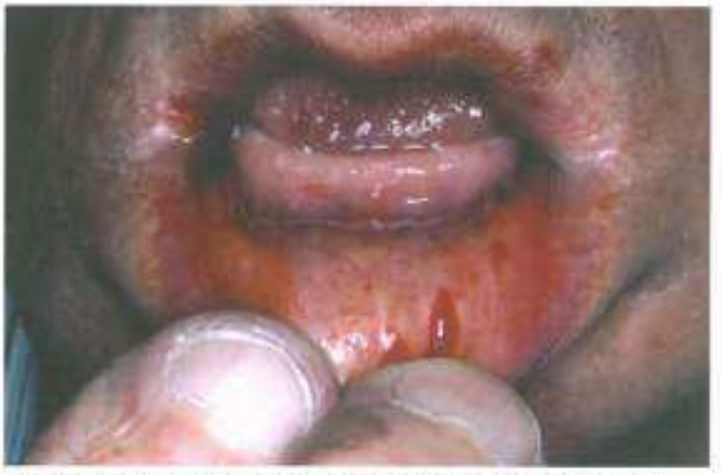


Fig. 22.68 Systemic amyloidosis. Petechiae and ecchymoses occur either spontaneously or after minimal trauma, including on the lips and in the mouth.

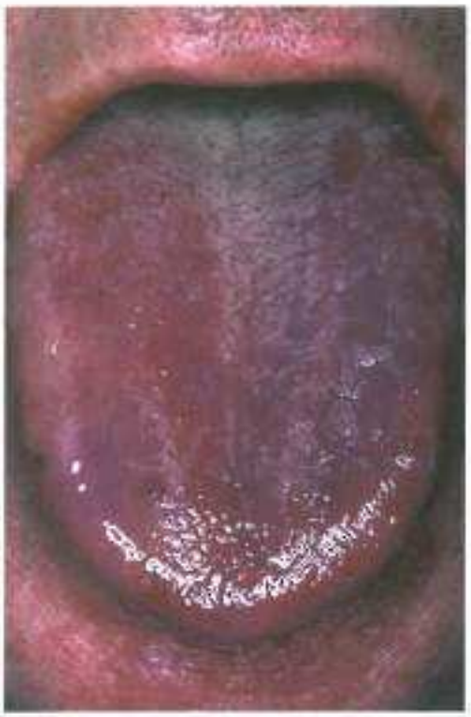


Fig. 22.69 Systemic amyloidosis. Macroglossia from infiltration with amyloid is striking. Multiple myeloma is the commonest cause. (Courtesy of Prof. Hywel Williams.)

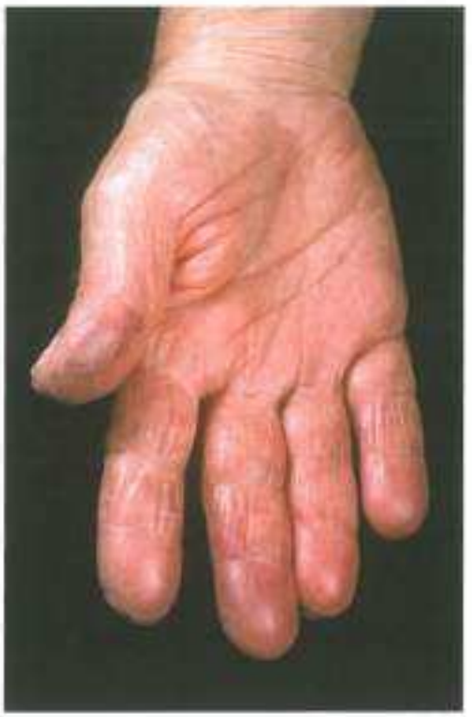


Fig. 22.70 Systemic amyloidosis. The fingers are thickened and the tips become soft, loose and redundant. (Courtesy of Prof. Hywel Williams.)

Distribution

The lesions occur particularly around the eyes, side of the neck, axillae, umbilicus and around the mouth and anogenital regions. The lips (Fig. 22.68), tongue (Fig. 22.69) and buccal mucosae are usually involved. There is thickening of the fingers and the skin becomes soft, loose and redundant at the fingertips (Fig. 22.70). The nails may be involved and may be the presenting feature (Figs 22.71 and 22.72).

Systemic signs of amyloidosis

Extracutaneous associations include nephrotic syndrome, gastrointestinal bleeding, peripheral and autonomic neuropathies, arrhythmias, congestive cardiac failure, sicca syndrome, amyloid deposition in the soft tissues around the shoulders, a rheumatoid arthritis-like condition of the small joints and coagulopathies secondary to amyloid infiltration of the liver.

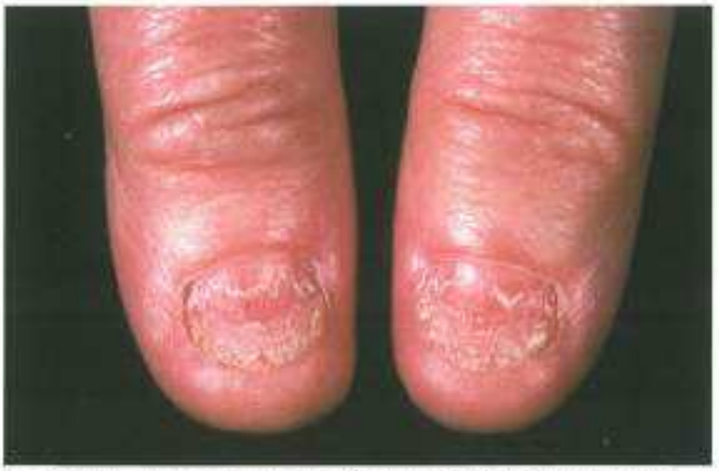


Fig. 22.71 Amyloidosis of the nails. She presented with thin and dystrophic nails. A clinical diagnosis of atypical lichen planus was made but biopsy was performed and deposits of amyloid were found due to myeloma.

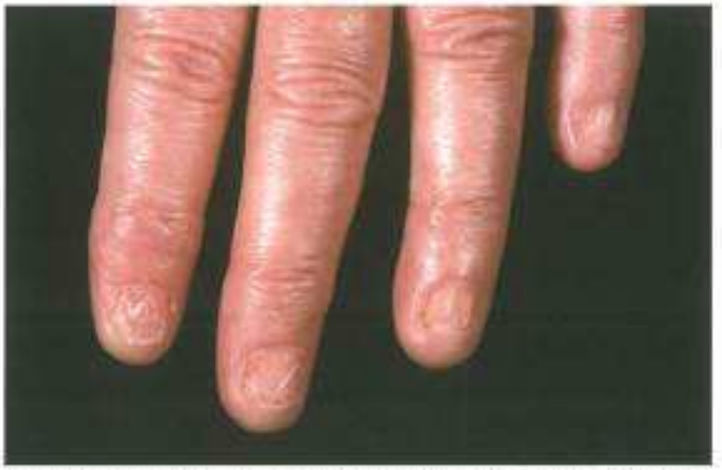


Fig. 22.72 Amyloidosis of the nails. All the nails are affected due to infiltration of the underlying nail bed by amyloid. The nail plate is damaged and does not form properly.

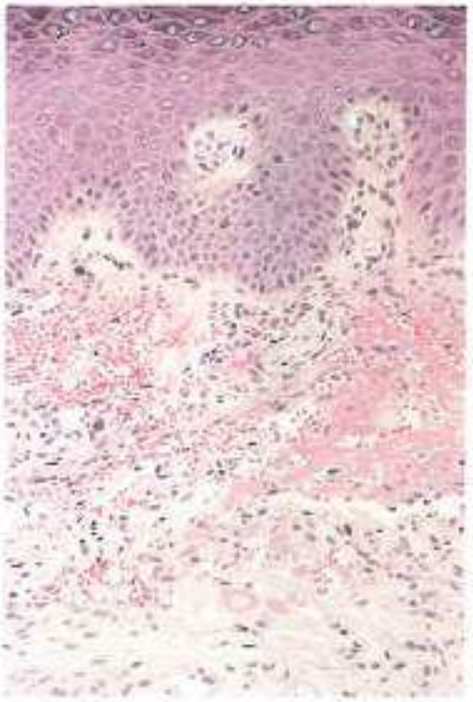


Fig. 22.73 Systemic amyloidosis. Abundant amyloid is present as pink amorphous material adjacent to the superficial vasculature. Note the purpura (extravasation of red blood cells).

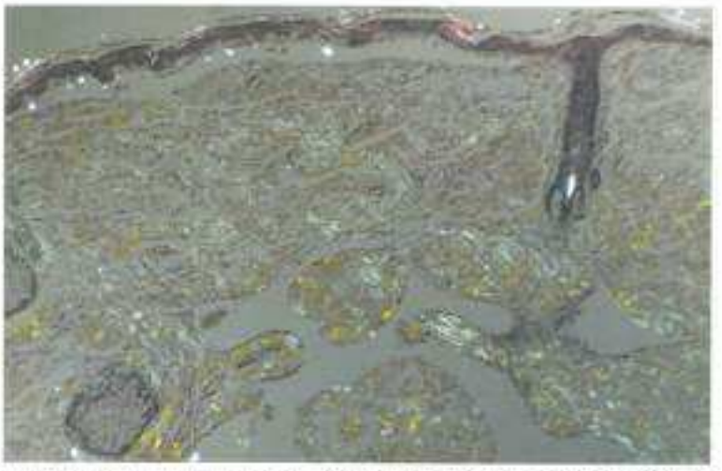


Fig. 22.74 Systemic amyloidosis. Apple-green birefringence is demonstrable in the amyloid in the dermis under polarized light.

Management

A skin biopsy should substantiate the diagnosis (Fig. 22.73). Positive staining occurs with Congo red and apple-green birefringence may be seen under polarized light (Fig. 22.74). AA loses its staining with Congo red after pretreatment with potassium permanganate, which AL does not. There are a variety of antisera to the proteins that may be used. PAS and methyl violet stains may also be positive. The radiolabelled SAP imaging technique using 123 I-SAP is an effective screen for amyloid deposition. In addition, bone marrow aspiration, immunoelectrophoresis of the serum and concentrated urine and skeletal survey are all helpful in the diagnosis of associated plasma cell dyscrasia. Amyloidosis is usually diagnosed too late and the prognosis is not good but myeloma-associated amyloid is treated with dexamethasone, cyclophosphamide, thalidomide, lenalidomide, bortezomib or high-dose melphalan. Autologous bone marrow transplantation has been tried. Death is usually a result of cardiac or renal failure.

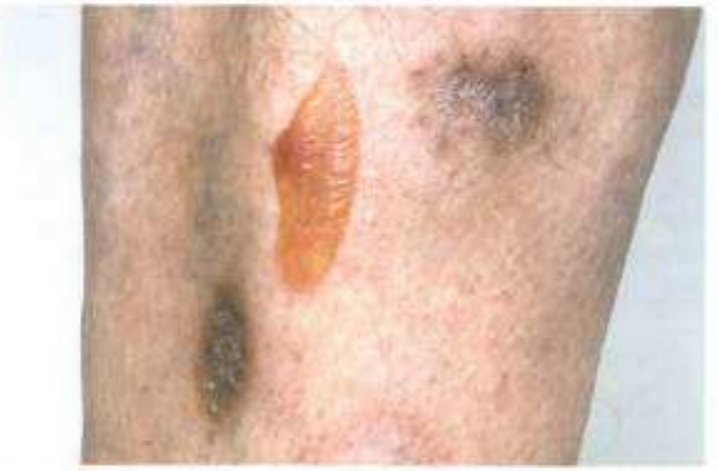


Fig. 22.75 Diabetic dermopathy. Pigmented atrophic macules and patches are common on the shins and may be associated with blisters (bullosis diabeticorum).

Endocrine abnormalities

DIABETES MELLITUS

The common cutaneous complications of diabetes are:

- **Infections** Candidiasis, particularly genital, is a common presentation of diabetes in older women. Erythrasma is more common. Tinea is probably not but should be treated because it does represent a potential portal for bacterial infection. Pyodermic infections may not be that common but may be more severe than in normal subjects.
- **Atherosclerosis** may lead to ischaemic changes in the skin, and ulceration. Blisters may occur on the soles of the feet and the plantar surfaces of the toes, probably secondary to the atherosclerosis.
- **Neuropathy** may lead to trophic changes and involvement of the autonomic nervous system reduces sweating of the lower extremities and causes dryness and fissuring; often there is compensatory sweating, often gustatory.
- **Generalized pruritus** may occasionally be a presenting feature.
- **Exanthematic and urticarial eruptions** may develop as a reaction to oral hypoglycaemic agents; chlorpropamide in particular may produce a phototoxic eruption, and alcohol-associated facial flushing.
- **Diabetic sclerodactyly** In young diabetics, the skin particularly over the dorsum of the hands may be quite thick, tight and waxy and the finger joints may be stiff in association.
- **Scleredema of Buschke** (Fig. 21.55)
- **Kyrle's disease** (Fig. 20.64)
- **Eruptive xanthomatosis** (Fig. 22.51)
- **Diabetic shin spots** or *diabetic dermopathy*. Multiple, asymptomatic, irregularly shaped, discrete, atrophic, brown macules resembling scars are common and occur in crops on the shins. Histologically, the arterioles and capillaries in the dermis show intimal thickening and deposition of PAS-positive fibrillary material in the vessel walls. There is often evidence of significant microangiopathy elsewhere. The macules may occur in association with blisters and this is known as *bullosis diabeticorum* (Fig. 22.75).
- **Haemochromatosis** A bronze pigmentation of the skin due to a mutation in HFE resulting in excess iron stores and cirrhosis, cardiac dysfunction and diabetes. The pigmentation, however, is secondary to melanin, not iron. It is also a risk factor for porphyria cutanea tarda.

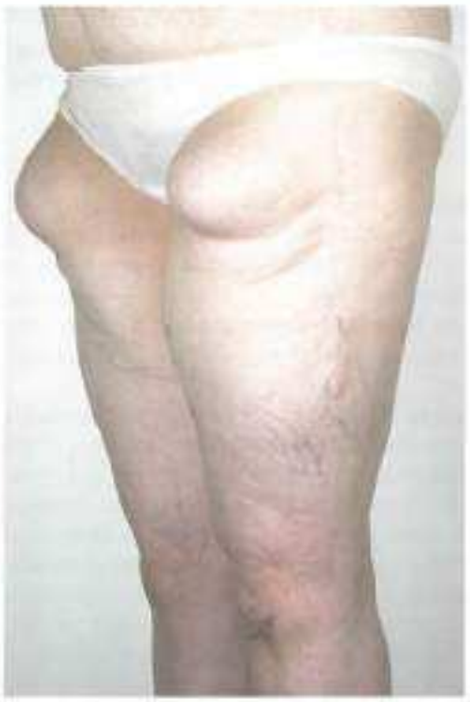


Fig. 22.76 Fat hypertrophy. This results from repeated injections of insulin into the same site, which stimulates the growth of adipose tissue. (Courtesy of Dr Peter Watkins.)

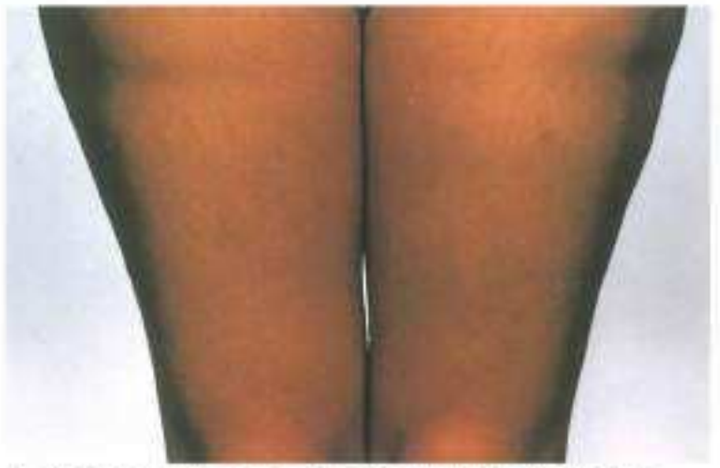


Fig. 22.77 Lipoatrophy semicircularis. Symmetrical asymptomatic linear horizontal depressions caused by loss of fat occur on the anterolateral thighs. The cause is unknown. It is more common in women and may be secondary to trauma.

- **Lipoatrophy** of the skin has resulted from insulin injections but is unusual now that more highly purified insulin preparations are used. There is a depression of the skin of the arms and thighs particularly in children and young women.
- **Lipohypertrophy** (Fig. 22.76) may also occur, particularly in males because of subcutaneous deposition of fat in sites that are used repeatedly for injections. It is probably caused by insulin-induced stimulation of adipose tissue growth. It should be distinguished from *lipoatrophy semicircularis*, where semicircular linear depressions occur around the thighs (Fig. 22.77), possibly secondary to trauma.
- **Acanthosis nigricans** may occur in association with insulin resistance. Insulin resistance is defined as the requirement for 200 units or more of insulin to control hyperglycaemia and prevent ketosis. It may occur in the absence of overt diabetes mellitus. It results from a failure occurring either before, at or after the insulin receptor. Antibodies to insulin or the production of mutated insulin accounts for the prereceptor abnormalities, and decreased numbers of receptors or diminished binding of insulin is responsible for the receptor abnormalities. The postreceptor insulin-resistant states result from abnormal signal transduction, particularly the failure to activate the receptor's tyrosinase kinase. Obesity is the most common cause of insulin resistance and there are a decreased number of receptors and postreceptor failure to activate tyrosinase kinase. Rare causes are the lipodystrophies (both generalized and partial and congenital or acquired), ataxia telangiectasia and Werner's syndrome. The last is an autosomal recessive disorder with a high incidence of hyperglycaemia despite increased plasma levels of insulin; the syndrome is associated with growth retardation, premature greying, alopecia, cataracts, hypogonadism and leg ulcers.

Type A and type B insulin resistance are relatively common. Type A results from mutations in the gene that encodes the insulin receptor and impairs insulin receptor signalling so that tyrosine kinase activity is either blocked or diminished. It is seen in young, black females, who are also tall, hirsute (Fig. 22.78) and have abnormalities of the reproductive tract including polycystic ovaries and other manifestations of androgen excess. The condition has been known as the HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans). Acanthosis nigricans also occurs in type B insulin resistance. This is seen in middle-aged females who produce spontaneous antibodies to the insulin receptor. Rituximab may be helpful. There are usually associated autoimmune disorders, including systemic lupus erythematosus, Sjögren's syndrome and, rarely, thyroid disorders and hypogonadism. Arthralgias and alopecia may occur. HAIR-AN syndrome is most common in black skins. The acanthosis nigricans is usually severe and generalized in the type A abnormality and its onset is in infancy or early childhood. It is less severe and less extensive in the type B and tends to reflect the activity of the underlying immunological disorder, which is most commonly systemic lupus erythematosus.

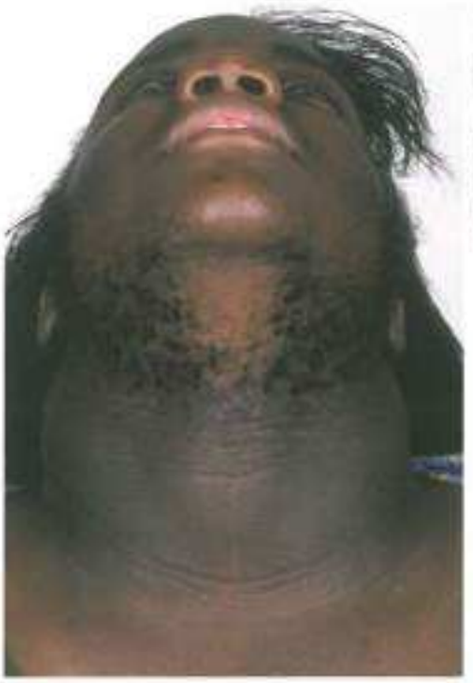


Fig. 22.78 HAIR-AN syndrome. Type A insulin resistance results in hirsutism, obesity, polycystic ovaries and pseudoacanthosis nigricans. It occurs in black-skinned females. (Courtesy of Dr A.C. Pembroke.)

- **Carotenaemia** (Ch. 27)
- **Vitiligo** (Ch. 27)
- **Necrobiosis lipoidica diabeticorum** (see below)
- **Granuloma annulare** (see below).

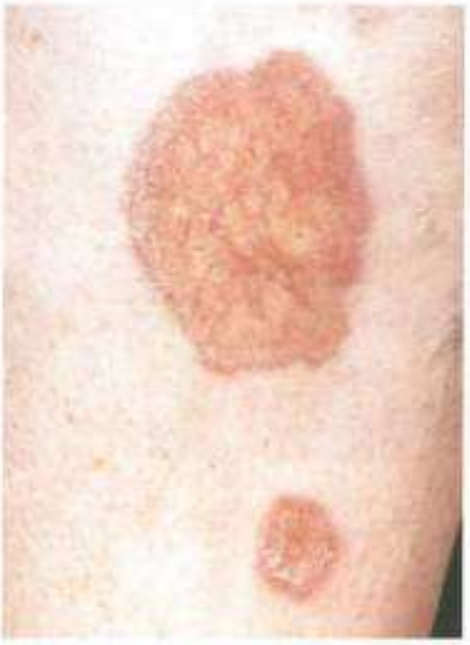


Fig. 22.79 Necrobiosis lipoidica. There are well-defined plaques with a yellow and red colour and prominent telangiectasia.

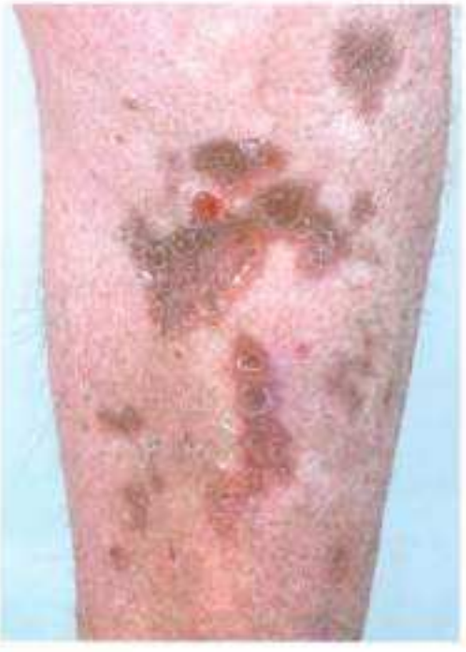


Fig. 22.80 Necrobiosis lipoidica. The shins are particularly affected, usually fairly symmetrically. It may or may not be associated with diabetes mellitus.

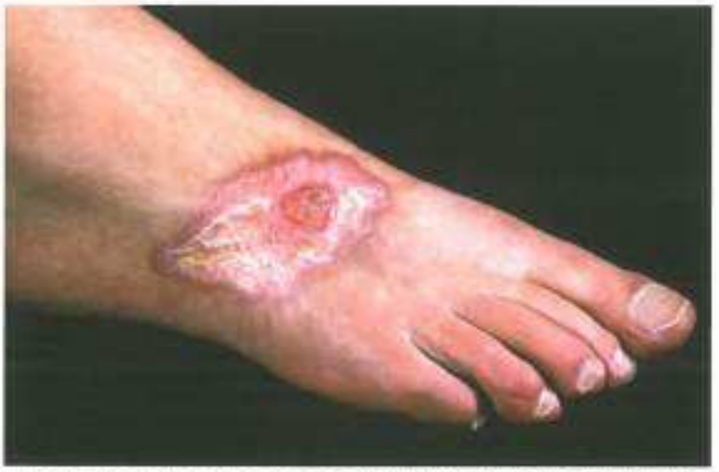


Fig. 22.81 Necrobiosis lipoidica. The dorsum of the foot is often involved. The lesions may ulcerate.

NECROBIOSIS LIPOIDICA DIABETICORUM

There are well-defined, yellowish plaques with a waxy consistency and surface telangiectasia; it occurs particularly on the lower limbs, sometimes in association with diabetes mellitus.

Aetiology

The cause is not known although it may be due to diabetic microangiopathy. It occurs in 0.3% of diabetics (both types) and is three times as common in women as men. The majority are less than 40 years of age. It is uncommon in black-skinned and Oriental patients. Although a significant proportion do not have overt diabetes mellitus, some have impaired glucose tolerance tests or a positive family history. About 15% develop diabetes years later.

Histologically there is a focal loss and marked alteration of collagen in the lower dermis. There is swelling, basophilia and distortion of the collagen bundles. This is known as necrobiosis. The diameter and cross-striations of the collagen fibres are irregular. There is loss and fragmentation of the elastic fibres. There are collections of inflammatory cells, which include epithelioid cells, histiocytes and multinucleate giant cells. Foam cells appear latterly and hence the term lipoidica. There is endothelial proliferation and occlusion of the arterioles and venules. There is, therefore, a granulomatous response to the degeneration of collagen, but whether this is secondary to underlying vascular disease or a primary degeneration of collagen is not known.

Clinical Features

Symptoms

Usually none but sometimes ulceration.

Morphology

More or less symmetrical, well-defined, brown-red or violaceous, waxy, irregular plaques with a telangiectactic and atrophic centre (Fig. 22.79).

Distribution

The shins (Fig. 22.80) and dorsa of the feet (Fig. 22.81) but occasionally the upper extremities, face, abdomen and hands are affected.

Management

In unusual sites, granuloma annulare and sarcoidosis must be considered. Treatment is not satisfactory. Intralesional steroids or superpotent steroids under occlusion can sometimes be of benefit. Ulcerated areas may be excised and grafted. Treatment of diabetes, if present, has no effect. Photodynamic therapy and infliximab have been tried.

GRANULOMA ANNULARE

A common condition of unknown aetiology of pink, ring-shaped lesions with individual red papules at the margins; it occurs particularly on the backs of the hands, ankles, knees and elbows and has a characteristic necrobiotic histology. Other forms, however, occur.

Aetiology

It may occur at any age but particularly in childhood and early adult life and in females. It is occasionally familial. Trauma, viruses (including HIV), allopurinol and sun exposure (when it is sometimes known as *O'Brien's actinic granuloma*, although some believe this to be a separate entity) have all been incriminated. It has histological similarities to necrobiosis lipoidica, and not infrequently there is an association with diabetes and sometimes a positive family history.

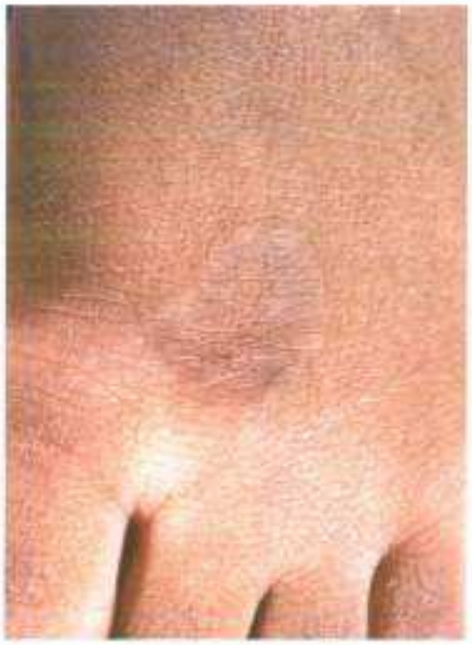


Fig. 22.82 Granuloma annulare. The margin of the eruption is most pronounced. It is common in children.

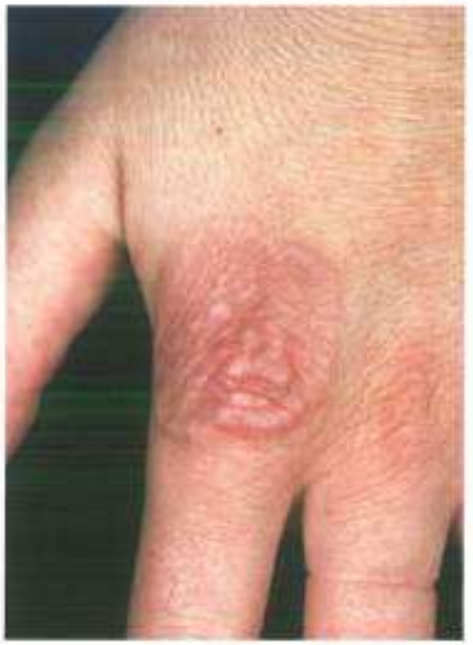


Fig. 22.83 Granuloma annulare. The margin is distinguished by individual papules, whereas the centre may be quite flat, although often there are papules within it. It is ring-shaped, but there is no scaling.

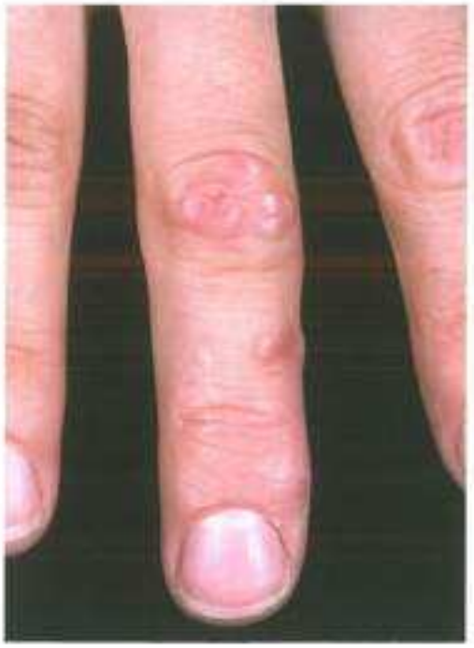


Fig. 22.84 Granuloma annulare. The margin of the eruption is made up of individual flat-topped papules. The knuckles are a common site.

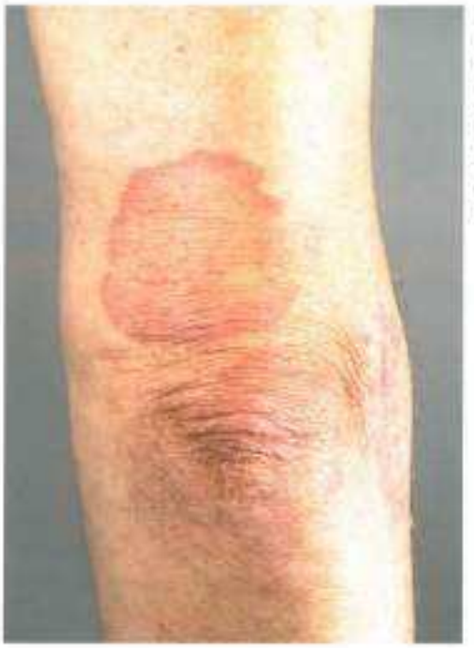


Fig. 22.85 Granuloma annulare. The lesions are annular and often mistaken for ringworm, although there is no surface scale. It may disappear spontaneously or respond to intralesional triamcinolone.

Clinical Features

Symptoms

The lesions may be tender if knocked.

Morphology and distribution

There are several variants.

- **Localized granuloma annulare** A well-defined, red, annular plaque (Fig. 22.82) with individual, flat-topped papules at the margin (Fig. 22.83). The plaques occur on the backs of the hands, particularly the knuckles (Fig. 22.84), feet, ankles, elbows (Fig. 22.85) and limbs, but may occur anywhere.
- **Subcutaneous granuloma annulare** Large, deep dermal or subcutaneous nodules occur on the palms, soles, fingertips (Fig. 22.86), toes and occasionally legs, buttocks, eyelids or scalp.

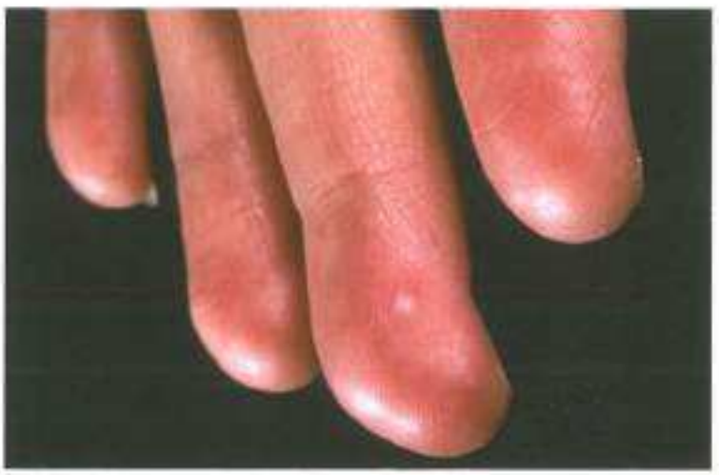


Fig. 22.86 Granuloma annulare. This nodular form is rare and painful. The middle fingertip is clearly involved. This patient was a diabetic.

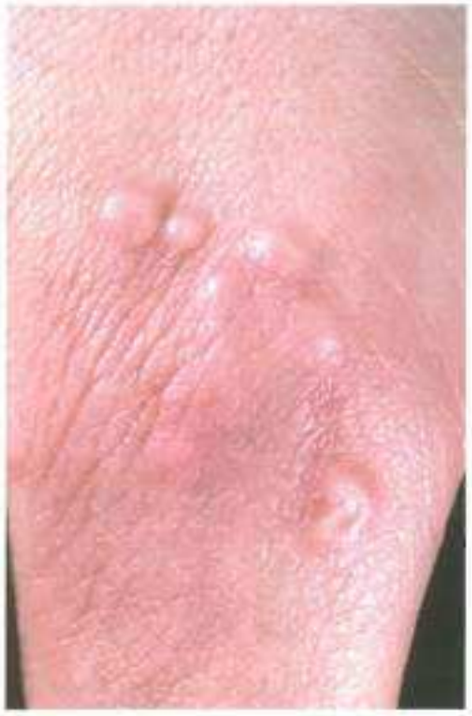


Fig. 22.87 Perforating granuloma annulare. Deep dermal or subcutaneous umbilicated papules or nodules may occur. A biopsy is necessary to establish the diagnosis.

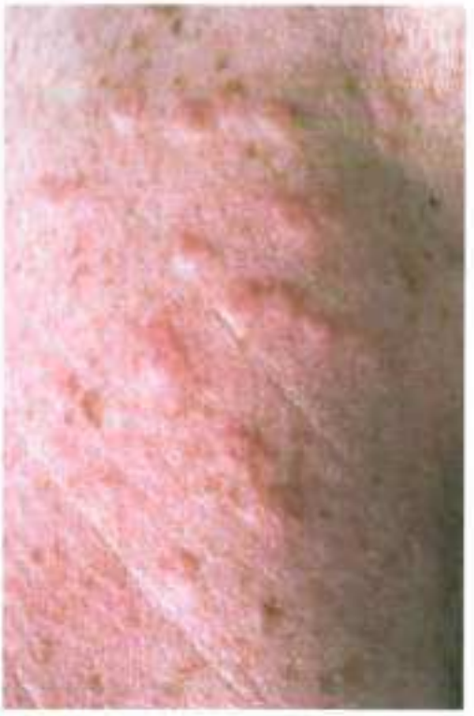


Fig. 22.88 Generalized granuloma annulare. The individual lesions are small papules, but the annular arrangement with more pronounced margin is discernible. This woman had non-Hodgkin's lymphoma, a rare but recognized complication.

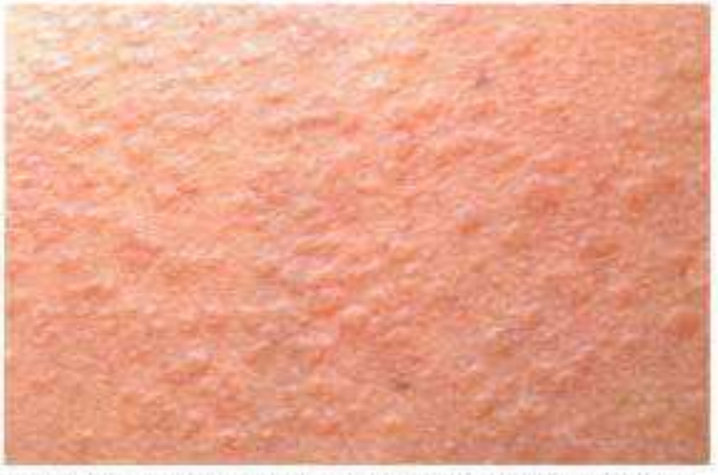


Fig. 22.89 Generalized granuloma annulare. The individual lesions are small macules or papules. (Courtesy of the Institute of Dermatology.)

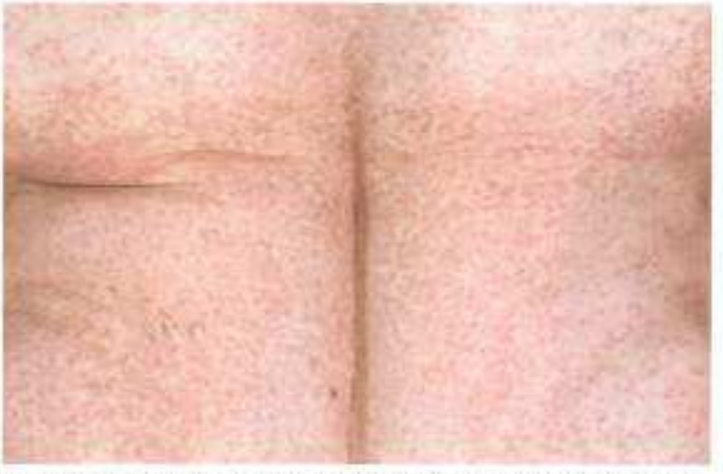


Fig. 22.90 Generalized granuloma annulare. The lesions are extensive on the trunk. (Courtesy of the Institute of Dermatology.)

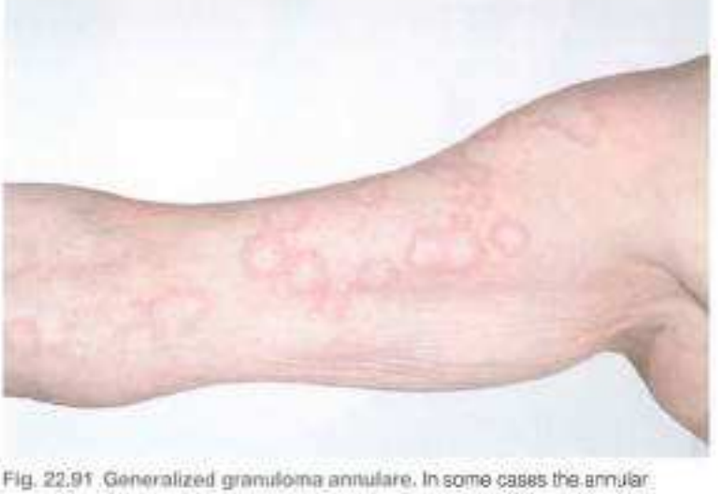


Fig. 22.91 Generalized granuloma annulare. In some cases the annular arrangement of the lesions is more obvious. It is more common in older patients.

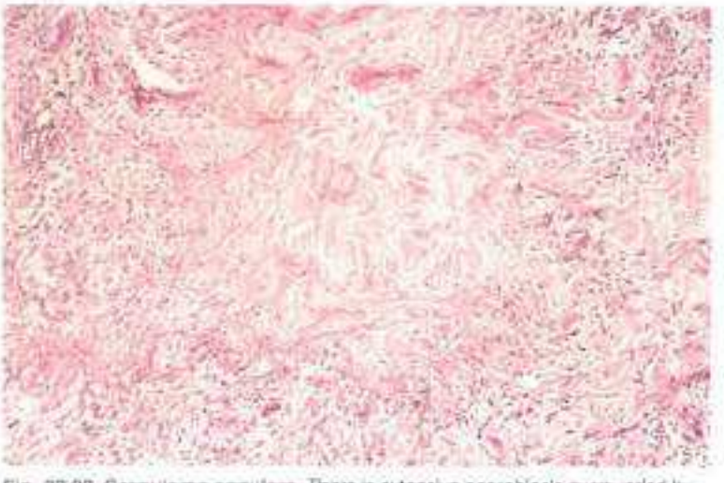


Fig. 22.92 Granuloma annulare. There is extensive necrobiosis surrounded by an ill-defined, palisaded histiocytic infiltrate.

Fig. 22.93 Cutis verticis gyrata. The scalp creases are accentuated and thrown into folds. These changes may occur in acromegaly, although in this case they were a result of a cutaneous T-cell lymphoma.

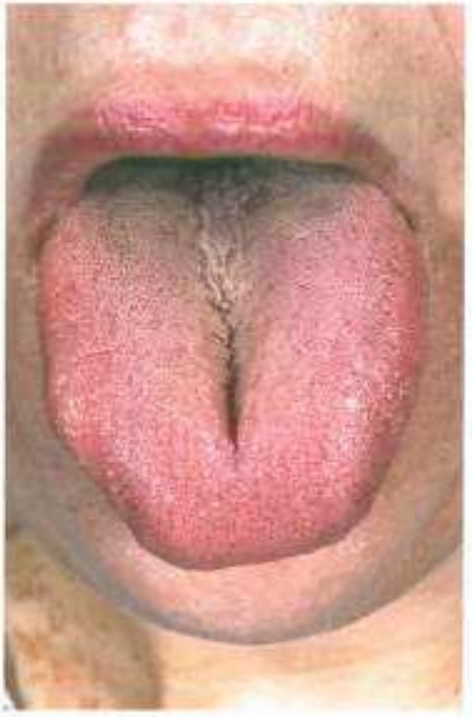


Fig. 22.94 Acromegaly. The tongue is large and often fissured.

- **Perforating granuloma annulare** Superficial small papules occur on the hands and fingers; there is a central umbilication (Fig. 22.87), plug or crust.
- **Generalized granuloma annulare** Many, small, flesh-coloured, yellow-red or brown macules and papules (Figs 22.88 and 22.89) occur. The annular configuration is less easy to discern. They are distributed extensively over the trunk (Fig. 22.90) and limbs (Fig. 22.91). They may be associated with HIV, lymphoid malignancy (including lymphoma and gastrointestinal stromal tumours) as well as diabetes.

Management

A skin biopsy will prove the diagnosis. The histology (Fig. 22.92) shows palisading of histiocytes around discrete foci of incomplete collagen degeneration (necrobiosis). Giant cells are usually absent. There is some perivascular lymphocytic cuffing and the changes are almost always confined to the dermis.

The lesions may disappear spontaneously, but the classical localized form responds well to intralesional steroids (although it often recurs). The atypical generalized variety may clear with superpotent steroids. Many other treatments have been used including psoralen ultraviolet A (PUVA) therapy, retinoids, ciclosporin, mycophenolate mofetil and antimalarials.

PITUITARY ABNORMALITIES

Acromegaly

Excess production of growth hormone (usually from an eosinophilic adenoma of the pituitary) results in a hyperplasia of both the epidermis and the dermal appendages that is most pronounced in the dermis (probably because of increased amounts of glycosaminoglycans and water retention). The skin is thickened and has a doughy consistency, particularly on the face and extremities, especially the hands and feet. The facial, neck and scalp creases are accentuated and the facial features are coarse so that the patient has a scowling, sombre appearance. The eyelids are thickened and oedematous and the lower lips are large and protruding. The hands and feet are enlarged. The changes in the scalp are known as *cutis verticis gyrata* (Fig. 22.93). There is macroglossia (Fig. 22.94) and the nose is widened

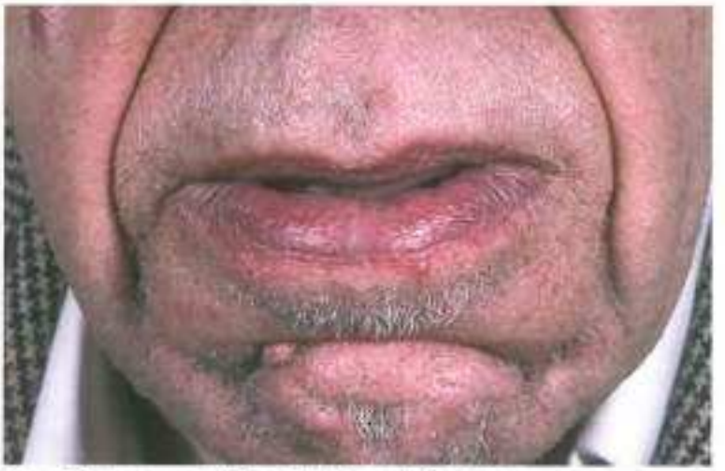


Fig. 22.95 Acromegaly. The skin is thickened. The facial creases are accentuated and coarse, producing a sombre appearance. The lower lips are large and protruding.

into a triangular shape. The ears are large and triangular. The finger pads are fleshy and the hands spade-like. The heel pads are thickened.

The pores are widened and the sebaceous glands are enlarged but acne is unusual. There is hyperhidrosis owing to enlarged sweat glands and the patients may have an unpleasant odour because of the increase in size of the apocrine glands. The body hair is coarse, particularly in the scalp; however, in the later stages of the disease when gonadotrophin levels decrease, body hair is diminished and becomes fine, silky and sparse. There is moderate darkening of the skin and an increase in skin tags and fibromas; acanthosis nigricans occurs since growth hormone antagonizes the action of insulin. The nails are thickened and hard.

The most striking effects are on bone and cartilage and there is prognathism (Fig. 22.95), frontal bossing, widely spaced teeth and increase in the size of the hands, feet and scalp. There are also local effects of the tumour including headaches and visual disturbances and secondary effects resulting from hypothyroidism, diabetes and hypogonadism.

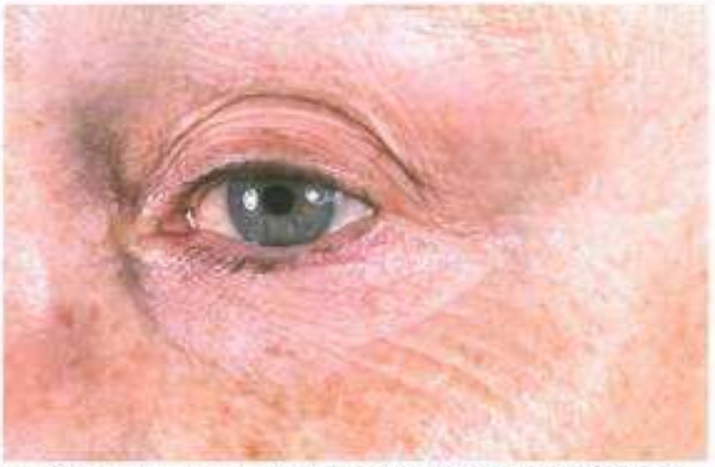


Fig. 22.96 Panhypopituitarism. There is a fine wrinkling around the eyes. The skin is pale because of diminished melanin production, and sunburn may be severe.

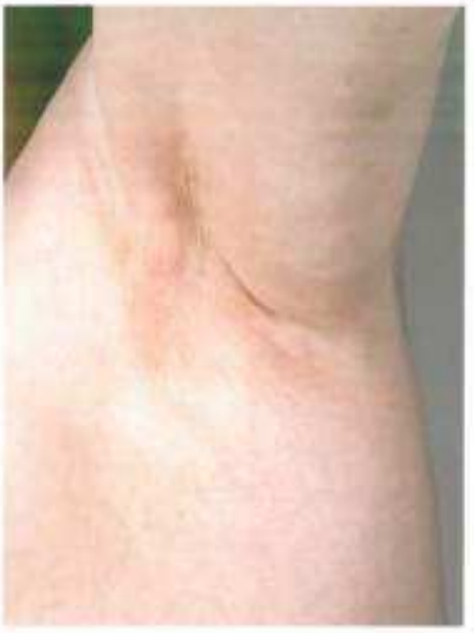


Fig. 22.97 Panhypopituitarism. Diminished growth of axillary hair is an early sign.

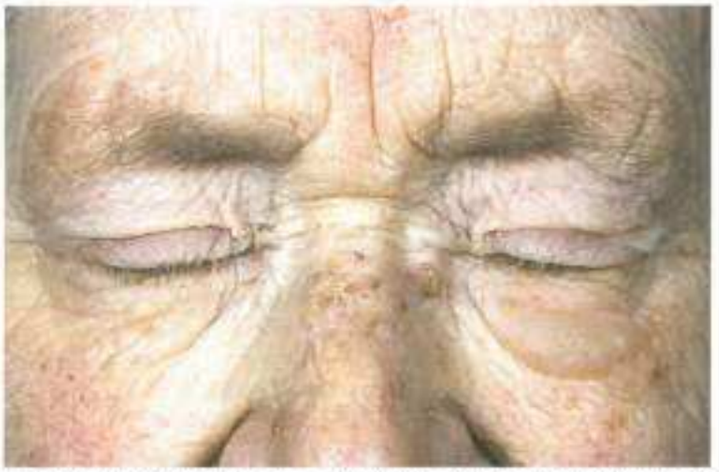
Panhypopituitarism

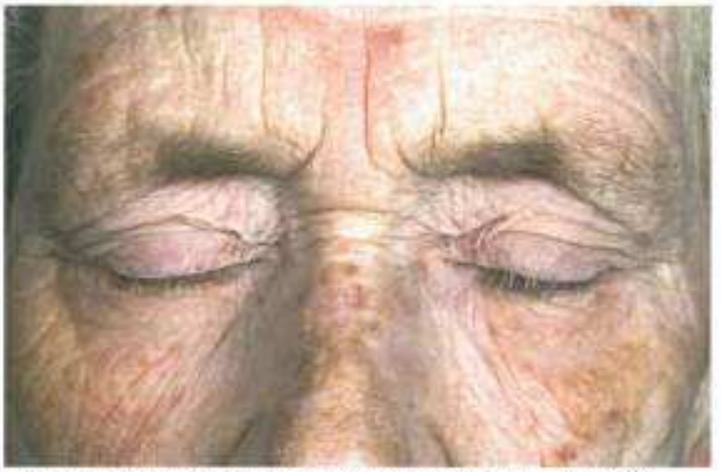
The failure of the elaboration of the pituitary hormones may result from a postpartum haemorrhage (Sheehan's syndrome), tumours of the pituitary and craniopharyngiomas, neoplastic invasion, Langerhans' cell histiocytosis, chronic infection (particularly syphilis and tuberculosis) and sarcoidosis. Melanin production is diminished because of the failure of ACTH and/or melanocyte-stimulating hormone. These patients are susceptible to severe sunburn as a result. The skin is pale, secondary to anaemia and reduced cutaneous blood flow. There is also occasionally increased carotene accumulation in the stratum corneum, producing a yellowish appearance. There is some dryness and puffiness of the skin, rather similar to that of myxoedema but not as gross because the thyroid gland, in common with other endocrine organs, has a baseline output of hormones of its own. There is marked decrease in facial folds and fine wrinkling around the eyes and mouth (Fig. 22.96). There is loss of body hair uniformly, and loss of axillary hair is an early sign (Fig. 22.97). There is loss of beard hair, although it is not total, and many patients remark that there is a decreased need to shave. The scalp hair is fine, dry and generally thin. There is a reduction in sweat production and in the size of the sebaceous glands. The nails grow slowly and are fragile, thin and opaque.

THYROID DISEASE

Hypothyroidism

Hypothyroidism results from the deficient production of thyroxine, either because of loss of function in thyroid tissue or its biosynthesis or inadequate stimulation of the gland due to pituitary or hypothalamic failure. The most striking feature is a boggy, non-pitting oedema of the face, particularly around the eyes (Figs 22.98 and 22.99), producing a puffy, doughy appearance and a general lack of expression. Hands and feet are also similarly affected. This 'myxoedema' results from the dermal accumulation of mucopolysaccharides caused by reduced degradation of hyaluronic acid, which binds water in the ground substance. The nose is broad, the lips are thickened and there is a smooth macroglossia. Protein extravasation and reduced lymphatic drainage increase the oedema. The skin is cool because of reduced cutaneous blood flow and core temperature, dry because of reduced sweat and sebaceous gland secretion and thickening of the epidermis, and pale (Fig. 22.100) because of anaemia, oedema and diminished blood flow. There is often a yellow tint to the skin from hypercarotenaemia secondary to the restricted capacity of the liver to form vitamin A. The scalp and body hair is dry, brittle and tends to fall out, often causing a diffuse or partial alopecia. The rate of hair growth is





Figs 22.98 and 22.99 Myxoedema. The skin is coarse, dry and somewhat yellow. The hair lacks lustre and falls out. There is oedema around the eyes (Fig. 22.98), which returns to normal (Fig. 22.99) with therapy.

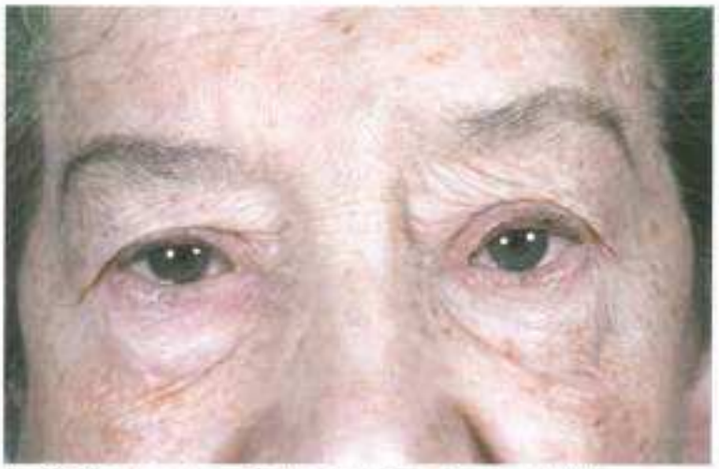


Fig. 22.100 Myxoedema. The skin is pale. There is a general lack of expression. There is puffiness around the eyes. The nose is broad.

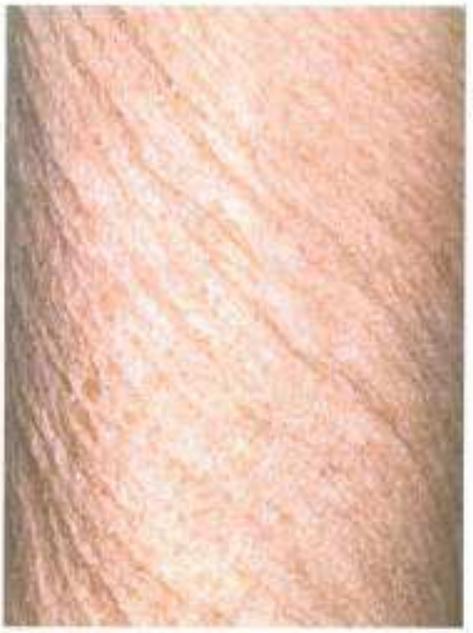


Fig. 22.101 Myxoedema. The skin is dry and there is a fine scaling. It may lead to eczema craquelé.

decreased and the lateral third of the eyebrow may be thinned or missing. Long lanugo-like hair may occur, particularly in children on the back. The nails are brittle and grow slowly, and there are often longitudinal transverse ridges. Wound healing is impaired and there is a tendency to purpura and ecchymoses secondary to subnormal levels of clotting factors. Separation of the elastic tissue and collagen by the oedema also results in lack of support of the blood vessels. There is a fine scaling of the trunk and limbs (Fig. 22.101) and eczema craquelé may occur.

Hyperthyroidism

Thyrotoxicosis results from excess production of thyroxine secondary to Graves' disease (Fig. 22.102), toxic nodular goitre in the initial phase of subacute thyroiditis or excess ingestion.

The skin is warm because of the cutaneous vasodilatation from the hyperdynamic circulation, moist because of excess sweating (particularly on the palms and soles) and smooth. There may be palmar erythema, facial flushing and telangiectasia. The hair is fine and friable. The fingernails grow rapidly, are soft and break easily. Onycholysis may occur. Occasionally there is diffuse hyperpigmentation. Pruritus, dermographism and urticaria are sometimes present. Vitiligo and alopecia may be associated with the autoimmune forms (Graves' disease and Hashimoto's thyroiditis).

Periosteal new bone formation (Fig. 22.103) may occur along the digits (thyroid acropathy), simulating clubbing, in association with exophthalmos, hyperthyroidism and pretibial myxoedema.

PRETIBIAL MYXOEDEMA

An infiltration of dermal skin with mucin, particularly over the shins, probably because of excess hyaluronic acid deposition in association with Graves' disease.

Aetiology

The condition occurs in about 5% of patients with Graves' disease and exophthalmos. The patients, however, may be biochemically normal and the condition often appears after successful treatment of hyperthyroidism. Graves' disease is an autoimmune disorder caused by circulating immunoglobulins that bind to thyroid cells and stimulate production and secretion of thyroid hormones. Pretibial myxoedema is thought to be caused by antibodies, probably to fibroblasts, leading to a localized

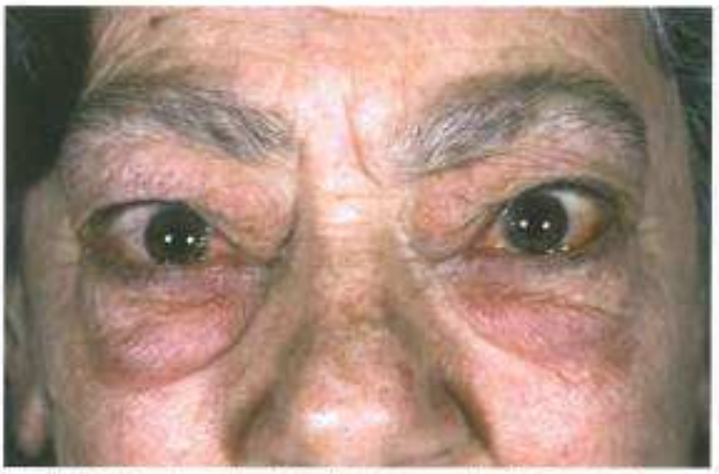


Fig. 22.102 Hyperthyroidism. Exophthalmos is prominent in Graves' disease. The skin is warm, moist and smooth. The hair is friable and may fall out. Onycholysis may occur.

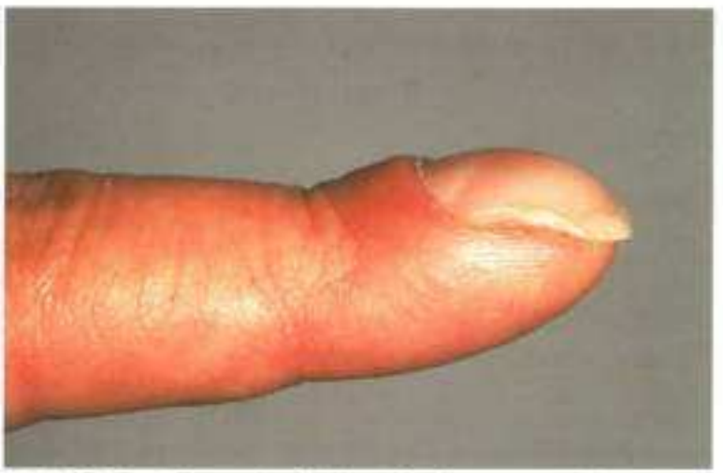


Fig. 22.103 Thyroid acropathy. Clubbing of the fingers may result from periosteal new bone formation in hyperthyroidism. (Courtesy of Dr T. Cundy, King's College Hospital, London.)

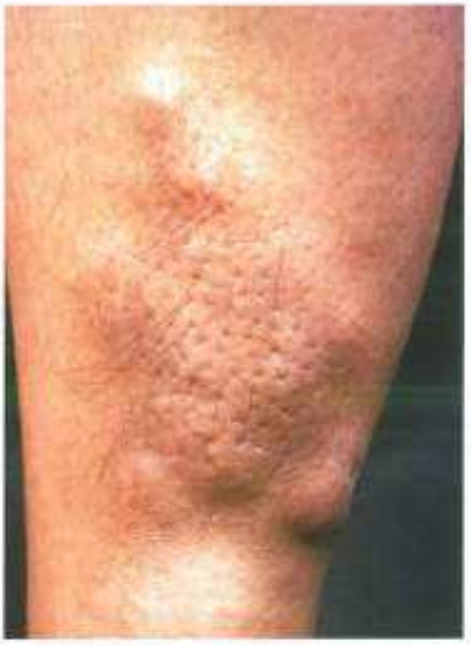


Fig. 22.104 Pretibial myxoedema. The plaque is raised and nodular in part. The follicular orifices are petulous ('peau d'orange' appearance) and there is hypertrichosis. It is much more common in women in early middle age. (Courtesy of St Mary's Hospital, London.)

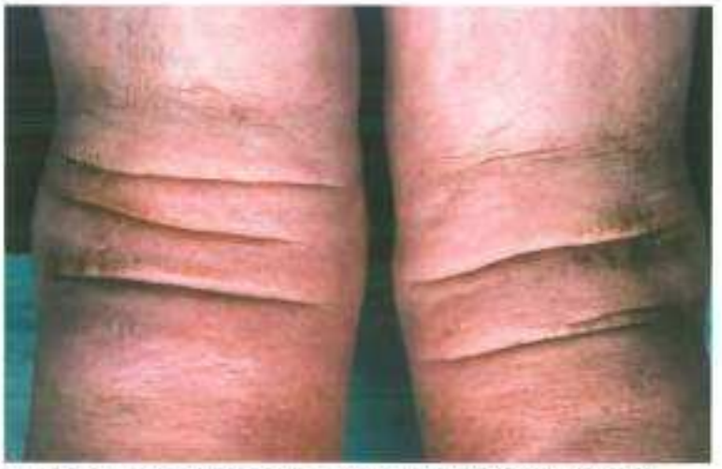


Fig. 22.105 Pretibial myxoedema. This woman with Graves' disease (Fig. 22.102) also had the verrucous form of pretibial myxoedema, giving an appearance simulating elephantiasis.

antigen–antibody reaction that causes increased hyaluronic acid production and associated fluid retention. Thyroid-stimulating globulin (formerly known as LATS) and other non-IgG fibroblast-stimulating factors are present. The fibroblasts in the eye and pretibial dermis probably share the same antigenic sites with the primary target in the thyroid gland in Graves' disease. It may be that the lower legs are affected primarily because of the increased hydrostatic pressure. Histologically, there is separation of normal collagen by mucin.

Clinical Features

Symptoms

Unsightly changes on the lower legs.

Morphology

There is a well-defined thickening and oedema of the skin owing to infiltration of the dermis with mucin. The thickening is yellow or skin coloured with prominent hair follicles and associated hypertrichosis (Fig. 22.104), often giving rise to a *peau d'orange* appearance. In severe cases, verrucous changes simulating elephantiasis may occur (Fig. 22.105).

Distribution

Bilateral, particularly over the fronts of the shins but sometimes on the dorsum of the feet and calves.

Management

The differential diagnosis is chronic venous stasis. Histology may be helpful. The cutaneous changes do not necessarily respond to treatment of the thyroid disease but steroids either under occlusion or by injection may help.

ADRENAL DISEASE

Hypercortisolism

Hypercortisolism is caused by either a functioning tumour of the adrenal cortex or adrenal hyperplasia secondary to excess stimulation by ACTH from a pituitary tumour (Cushing's syndrome) or an ectopic neoplasm. Iatrogenic steroid therapy has made it commonplace. There is redistribution of the subcutaneous fat. The patient has a round face with full cheeks ('moon facies'), fat in the supraclavicular fossae, over the dorsal cervical vertebra ('buffalo hump') and around the pelvic girdle. However, there is loss of subcutaneous fat in the extremities and muscle wasting so the limbs appear very thin in comparison. There is loss of height because of kyphosis, caused by compression fractures as a result of osteoporosis. All these features produce a very characteristic appearance.

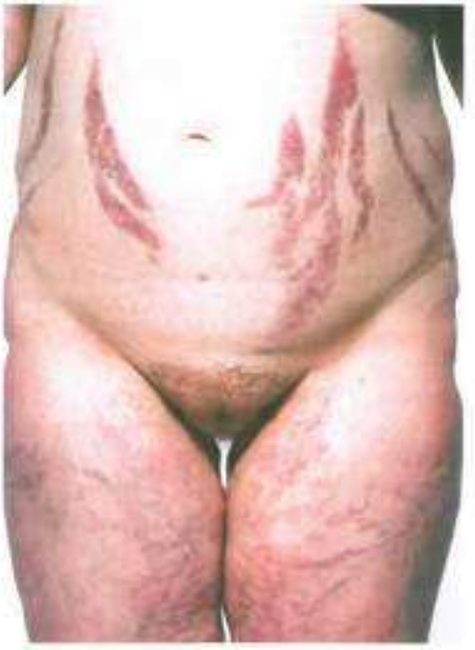


Fig. 22.106 Cushing's syndrome. The purple striae on the thighs and sides of the abdomen are characteristic. Note the atrophy and telangiectasia of the thighs.

The skin is atrophic, both in the epidermis, which is thin, shiny and has a slight scale, and the dermis. Collagen synthesis is inhibited and, histologically, individual collagen fibres are not united into bundles properly. There is reduction in the elastic tissue ground substance and in mucopolysaccharides. The skin is friable, easily damaged and there is reduced wound healing. It is transparent and ecchymoses are common at the sites of trauma, including venepuncture sites. There are striae, particularly on the flanks of the abdomen, arms and thighs (Fig. 22.106), which are different from those of adolescence (Fig. 22.107), pregnancy or obesity in that they have increased depth and breadth and a more livid colour, rather

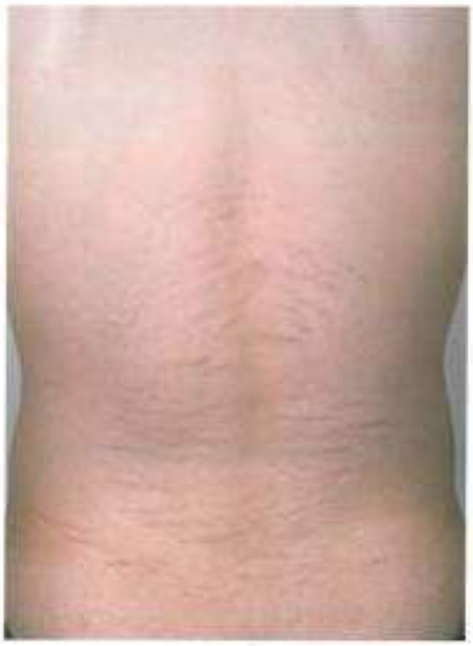


Fig. 22.107 Physiological striae. These occur during adolescence and are associated with a rapid growth spurt.

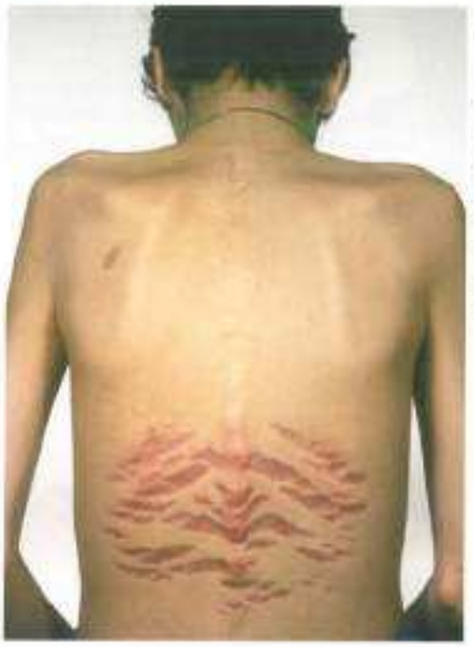


Fig. 22.108 Striae caused by Marfan's syndrome. Striae are wide, prominent and common in this skeletal, cardiovascular and ocular autosomal dominant connective tissue disorder syndrome. It is caused by mutations in the gene encoding fibrillin-1. The skin is also thin and slightly hyperextensible.

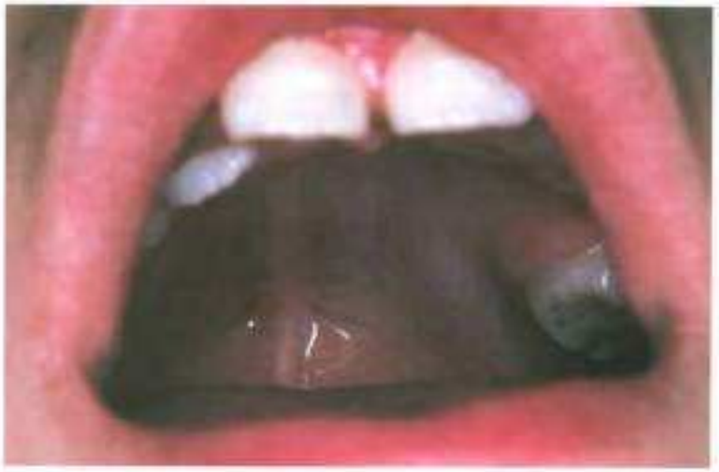


Fig. 22.109 Marfan's syndrome. A high arched palate is characteristic of this autosomal dominant disorder of fibrillin-1, an important component of elastic fibres.

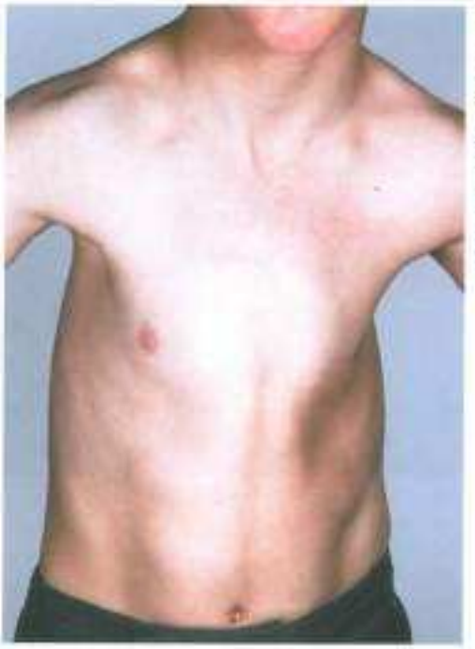


Fig. 22.110 Marfan's syndrome. The decreased or aberrant deposition of elastic fibres affects the skin, eyes, cardiovascular syndrome and skeleton with arachnodactyly and a characteristic habitus and pectus excavatum as shown here.

like, but not as wide as, those of Marfan's syndrome (Figs 22.108, 22.109 and 22.110). The skin is paper thin and ulcerates easily from minor trauma. Topical steroids produce similar changes (Fig. 5.49) The face is often plethoric because of polycythaemia or erythrocytosis. As a result of decreased vascular tone, there is cutis marmorata, particularly of the legs.

The patient is more susceptible to cutaneous infection. Pityriasis versicolor, *Trichophyton rubrum* infection and candidiasis are common. Acne is common either as an exacerbation of previous acne vulgaris or in a monomorphic papulopustular form known as steroid acne. This is caused by abnormal follicular keratinization and a resultant weakened follicle wall. The lesions occur on the trunk, shoulders and arms particularly and do not affect the face very much. Since there is no bacterial involvement, the acne responds better to topical tretinoin than to antibiotics. Hypertrichosis is common although in iatrogenic Cushing's syndrome there is a predominance of lanugo type hairs. If hirsutism is pronounced, it is likely that an adrenal virilizing tumour is present. There may be an increase in generalized pigmentation in Cushing's syndrome and it is particularly marked if adrenalectomy has been performed (Nelson's syndrome). Acanthosis nigricans is usually mild.

Adrenal Insufficiency

Primary adrenal cortical failure is caused by an infection such as tuberculosis, surgery or autoantibodies. It may, however, be secondary to inadequate stimulation by ACTH or abnormal biosynthesis of glucocorticosteroids, as in the adrenogenital syndrome. The physical signs vary depending on the cause, but in all cases there is decreased production of glucocorticosteroids and also of adrenal androgens, except in the adrenogenital syndrome. The striking physical sign of glucocorticosteroid deficiency is an increase in pigmentation due to the MSH-like effect of

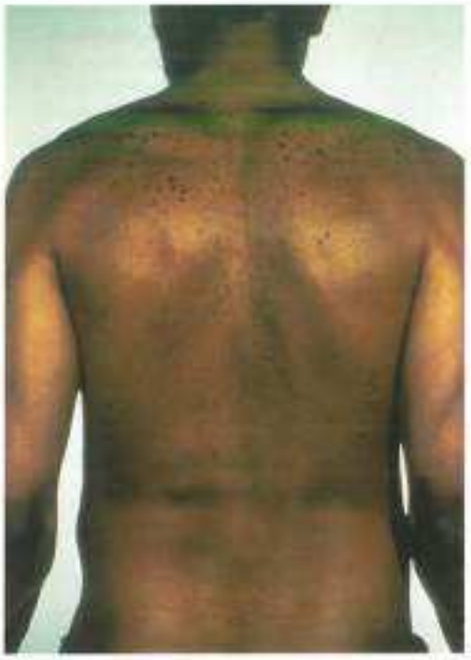


Fig. 22.111 Addison's disease. There is a striking, although insidious, increase in pigmentation. Lentigines (upper back) and naevi darken.

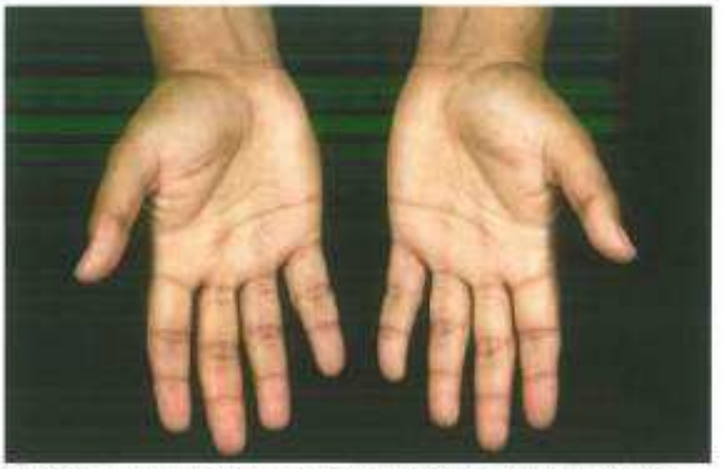


Fig. 22.112 Addison's disease. The palmar creases are pigmented in adrenal insufficiency.

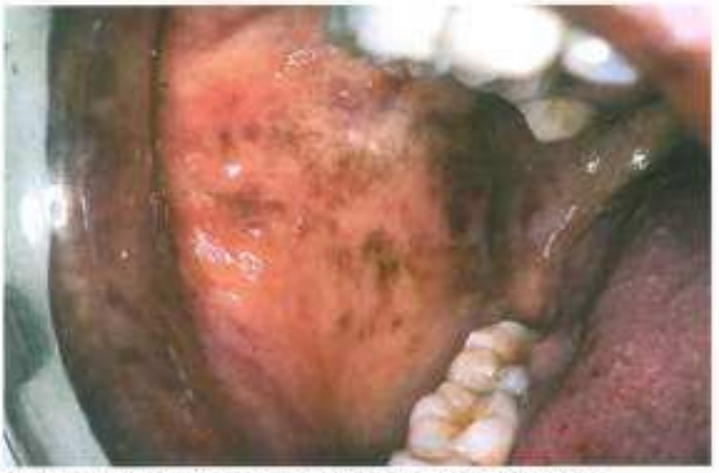


Fig. 22.113 Addison's disease. There is pigmentation of all mucous membranes, including the buccal mucosae.

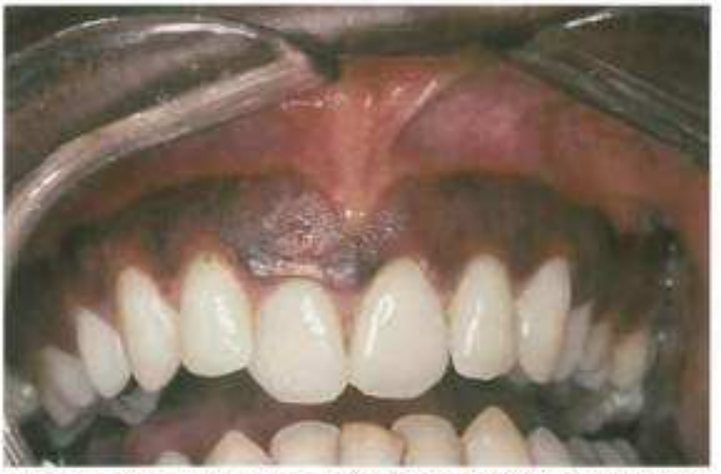


Fig. 22.114 Racial pigmentation. There is a diffuse hyperpigmentation affecting the gingiva. In black-skinned races, this is quite normal.

ACTH (Fig. 22.111). It is insidious initially and may not be noticed by the patient. Previous suntan fails to fade. The pigmentation is also increased on pressure points such as the knees, knuckles, ischial tuberosities and in intertriginous areas. There is darkening of the axillae, perineum, nipples and palmar creases (Fig. 22.112). This darkening is a specific sign, although it also occurs in pernicious anaemia and is quite normal in black skins. There is darkening of pre-existing naevi and appearance of new ones. The mucous membranes are pigmented, including the vagina, anus and mouth (Fig. 22.113). Such pigmentation is, however, normal in black skins (Fig. 22.114) although if extensive may suggest Addison's disease. The hair becomes darker and there are longitudinal pigmented lines in the nails. Pigmentation simulating adrenal insufficiency may occur in Laugier–Hunziker syndrome, where the patient is otherwise perfectly well.

The signs of androgen deficiency are loss of body hair. Postpubescent females lose their ambisexual hair, that is the hair in the axillae and in the lower pubic triangle, which is dependent upon adrenal androgens.

Vitiligo is seen in about 15% of patients with autoimmune Addison's disease.

Metabolic disorders

THE PORPHYRIAS

The porphyrias are a group of genetically determined inborn errors of metabolism caused by partial (otherwise it is fatal) enzyme defects in haem biosynthesis. Haem is a tetrapyrrole like chlorophyll and vitamin B_{12}. It is formed from glycine and succinyl coenzyme A in a complex eight-step series of intracellular decarboxylase and oxidative reactions (Table 22.1). The chromosome locations of these enzymes have all now been assigned. The reactions occur in the hepatocytes and erythrocytes. If an enzyme in the biosynthetic pathway is defective, there will be an accumulation of toxic porphyrin precursors or porphyrin by-products in the liver or blood. Certain porphyrins are photoactive and absorb light energy in the visible range (between 400 and 410 nm) to give unstable excited-state molecules. Most types are inherited, although the commonest (porphyria cutanea tarda) is acquired, and are associated with iron overload and liver disease. Disorders of porphyrin metabolism are categorized into whether the liver (the majority) or bone marrow (EPP and Gunther's) is the source of the substrate excess although, in reality, both organs contribute so they may be most usefully categorized into acute (constituting a medical emergency) and non-acute forms. There are four types of acute porphyria, where neurovisceral symptoms predominate:

- ALA dehydrogenase deficiency and
- acute intermittent (which do not have skin signs)
- hereditary coproporphyria and
- variegate porphyria (which may have skin manifestations).

Precipitating factors are poor diet (especially low intake of carbohydrates), drugs (particularly sulphonamides, barbiturates, female sex hormones such as progesterone, and hydantoins), alcohol, smoking and infection. The abdominal symptoms are recurrent severe colicky usually lower abdominal pain for which no cause is found. The urine is dark or red, and there is hypotension, tachycardia and constipation. The 5-ALA and porphobilinogen are raised in the urine and serum. Cutaneous changes always occur in the non-acute forms (Gunther's, EPP, PCT and hepatoerythropoietic porphyria).

TABLE 22.1 The Haem biosynthetic pathway and mechanisms of the porphyrias

Glycine + Succinyl Coenzyme A		
	ALA synthetase I	
ALA (Aminolaevulinic acid)		
Also known as porphobilinogen synthase	ALA dehydratase (ALA dehydratase porphyria)	Acute neurovisceral
Porphobilinogen (cytoplasm)		
Also known as hydroxymethylbilane synthase	Porphobilinogen deaminase (AIP)	Acute
Hydroxymethylbilane (cytoplasm)		
Also known as uroporphyrinogen cosynthase	Uroporphyrinogen III synthetase (Congenital EP)	Skin major source = bone marrow
Uroporphyrinogen III (cytoplasm)		
	Uroporphyrinogen III decarboxylase (PCT)	Skin
Coproporphyrinogen III (cytoplasm)		
	Coproporphyrinogen III Oxidase (coproporphyria)	Acute; may involve skin
Protoporphyrinogen IX (mitochondria)		
	Protoporphyrinogen oxidase (Variegate)	Acute; may involve skin
Protoporphyrin IX (mitochondria)		
Fe^{2+} →	Ferrochelatase (EPP)	Skin; source = bone marrow
Haem		

CONGENITAL ERYTHROPOIETIC PORPHYRIA

An extremely rare autosomal recessive disorder caused by defective uroporphyrinogen cosynthetase; it usually presents in infancy with red-stained diapers and results in photosensitivity, haemolytic anaemia, erythrodontia and bone abnormalities.

Aetiology

In 1911 Gunther described this mutilating photosensitivity. It is caused by defective activity of the fourth enzyme in haem biosynthesis: uroporphyrinogen cosynthetase. As a result, uroporphyrins and coproporphyrins, largely of the isomer I series, accumulate in the bone marrow, red cells, urine, bones and teeth. These porphyrin by-products are red-brown pigments and discolour the urine and redden the teeth. Uroporphyrinogen I is a photosensitizer, and subepidermal bullae are found histologically. Adult onset disease may be a manifestation of the myelodysplastic syndrome.

Clinical Features

Symptoms

Photosensitivity occurs (in infancy, childhood or even later). The porphyrins are excreted in the urine (Fig. 22.115), causing pink or red discoloration of the nappies (diapers).

Fig. 22.115 Erythropoietic porphyria (Gunther's disease). The urine turns red or pink and discolours the infant's nappy. This may be the presenting complaint.

Morphology

Blisters (Fig. 22.116) form, often containing pink fluid, that heal slowly, frequently with ulceration and scarring, leading ultimately to severe deformities with destruction of the nasal and auricular cartilage. Other acral tissue is affected. The distal phalanges may be resorbed (Fig. 22.117) and syndactyly and contractures occur. Scarring alopecia is common (Fig. 22.118).

Hyperpigmentation and hirsutism, particularly with long, dark lanugo-like hair, occurs particularly on the light-exposed areas.

Distribution

Light-exposed areas.

Systemic signs

Eye changes are common. These include photophobia, keratoconjunctivitis, ectropion, symblepharon and reduced vision.

As uroporphyrin I accumulates in the red blood cells, haemolytic anaemia, splenomegaly, porphyrin-rich gallstones and premature senescence of erythrocytes result. There is compensatory recruitment of erythroid precursors from the bone marrow into the circulation and the nucleated normoblasts in the peripheral blood fluoresce. The teeth also fluoresce as a result of deposition in the dentine (Fig. 22.119). Bone fragility may result in fractures and shortness of stature.

Management

The diagnosis is made by finding elevated levels of uroporphyrin I and coproporphyrin I in the urine and coproporphyrin I in the faeces. There is elevation of uroporphyrin I and protoporphyrin in the red blood cells and plasma. It is crucial to avoid sunlight. Opaque sunscreens that block visible light (e.g. those containing titanium dioxide) are mandatory. Splenectomy may decrease the rate of erythrocyte destruction and blood transfusion may be necessary. Recurrent skin infections, which are common, should be treated. The beneficial effects of bone marrow transplantation have been reported.

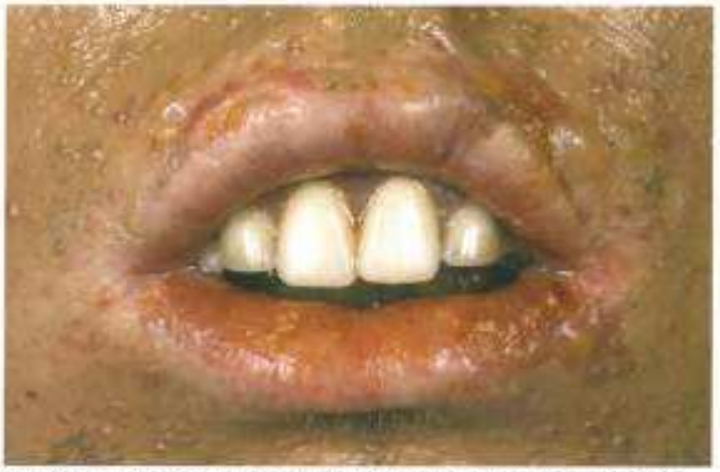


Fig. 22.116 Erythropoietic porphyria. Blisters occur on exposure to sunlight, which ulcerate, scar and mutilate.

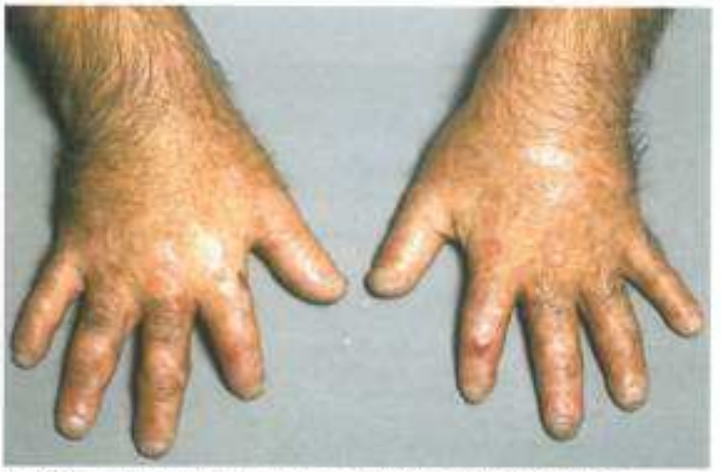


Fig. 22.117 Erythropoietic porphyria. The distal phalanges have been resorbed. There is scarring on the backs of the hands and fingers but the wrists (spared to some extent from light) are relatively normal.

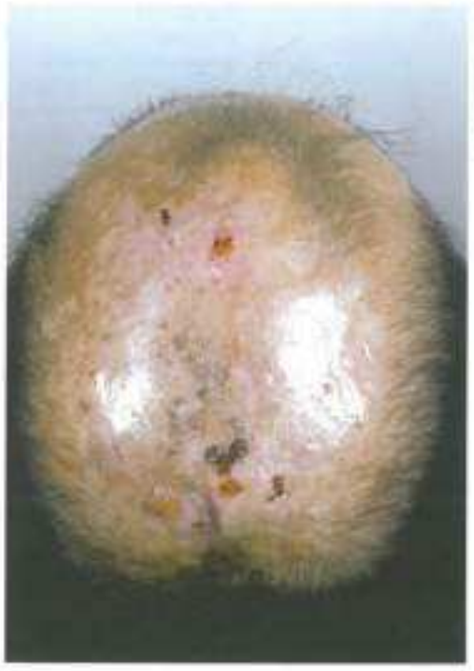


Fig. 22.118 Erythropoietic porphyria. The blisters heal slowly and often scar. Note the scarring alopecia.

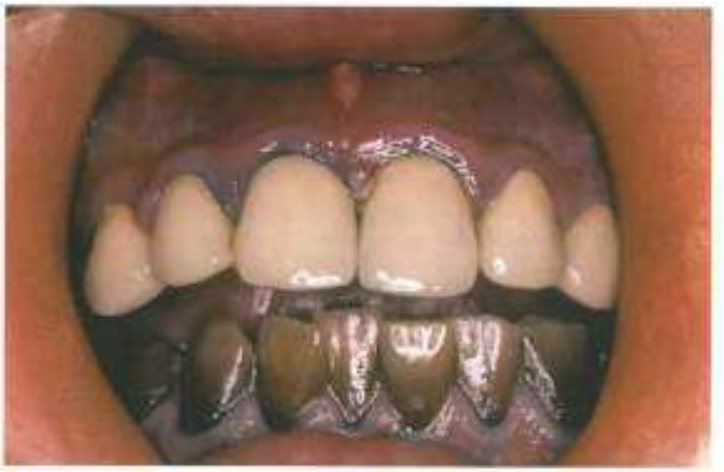


Fig. 22.119 Erythropoietic porphyria. The porphyrins are deposited in the dentine of the teeth (lower) and, consequently, false teeth (upper) are eventually required.

ERYTHROPOIETIC PROTOPORPHYRIA

A genetic disorder of ferrochelatase metabolism such that protoporphyrin accumulates in the skin, red cells, plasma and faeces, which leads to phototoxicity, cholelithiasis and potentially severe liver disease.

Aetiology

This disorder was first described by Magnus in 1961 and is relatively common. It is inherited as an autosomal dominant or recessive. There is partial deficiency of ferrochelatase (FECH), the eighth and ultimate enzyme in haem biosynthesis, which is located in the mitochondria and catalyses the insertion of Fe into protoporphyrin to form haem. It results in the accumulation of its substrate protoporphyrin, largely in the bone marrow although in some cases the liver is severely affected. The porphyrins become less soluble as their structure becomes closer to that of haem. Protoporphyrin is, therefore, strongly hydrophobic and is excreted, in the faeces rather than the urine. It was probably for this reason that the recognition of the condition was made so late in that no abnormal porphyrins are identified in the urine. The protoporphyrin in the red cells can be made to fluoresce in bone marrow or blood specimens. Histologically, damage occurs in the dermis and there is marked thickening of the blood vessels, which are surrounded by a hyaline-like material that stains positively with PAS.

Clinical Features

Symptoms

Itching, burning, smarting or stinging of the skin occurs within minutes of exposure to ultraviolet sunlight in childhood. This is often dismissed as hysterical as there may be no abnormal cutaneous signs.

Morphology

There is either nothing abnormal to see or erythema and mild oedema with occasional petechiae develop a few hours after exposure to the sun (Fig. 22.120). Chronically damaged skin may become thickened, leathery and aged, particularly over the backs of the hands and knuckles. Similar changes may occur on the face as well but superficial pitted and linear scars (Fig. 22.121) on the cheeks, forehead and nose are characteristic. Linear furrowing around the lips may also occur.

Distribution

Light exposed skin.

Systemic signs

Gallstones are common in the third or fourth decade. Protoporphyrin accumulation in the liver may result in cirrhosis and occasionally liver failure.

Management

The differential diagnosis is solar urticaria but there is minimal oedema and a rare drug (naproxen) sensitivity. The diagnosis is substantiated by the finding of protoporphyrins in the red blood cells (dietary haem may confound the diagnosis if stools are examined) and the ferrochelatase levels may be measured. Photoprotection is mandatory. Opaque topical sunscreens containing zinc oxide or titanium dioxide should be used. In some patients, photosensitivity is lessened by beta-carotene but it takes many weeks to have an effect. The patients are not usually anaemic but blood transfusion has been reported to be of benefit. The prognosis depends upon the severity of hepatocellular dysfunction and in severe cases, liver transplantation is the only resort.

PORPHYRIA CUTANEA TARDA

A photosensitivity caused by accumulation of water-soluble uroporphyrins and coproporphyrins as a result of a partial uroporphyrinogen decarboxylase deficiency which can result in liver damage.

Aetiology

This is the commonest of the porphyrias and the only one that has both a familial and acquired form. Not all individuals carrying the heterozygous genetic defect manifest the disease. For disease expression, it appears to require additional factors, which include alcohol, oestrogens, viruses, particularly hepatitis C and maybe HIV (possibly an epiphenomenon of hepatitis C), iron, lead and certain aromatic hydrocarbon hepatotoxins. The last was responsible for an epidemic in Turkey when wheat seed, treated with hexachlorobenzene (as a fungicide) and originally intended for planting, was used for food production during a period of relative famine because it arrived too late in the season for sowing.

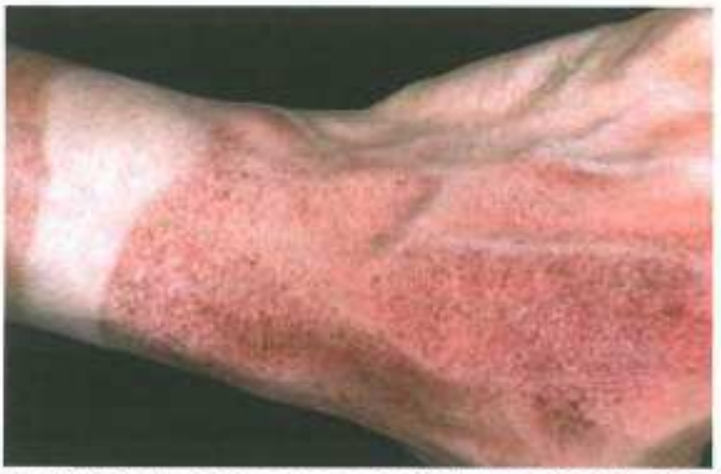


Fig. 22.120 Erythropoietic protoporphyria. Despite the complaint of burning skin, there may be no abnormal physical signs. However, in some, erythema, petechiae and oedema may develop in sun-exposed skin (note the watch has protected the wrist).

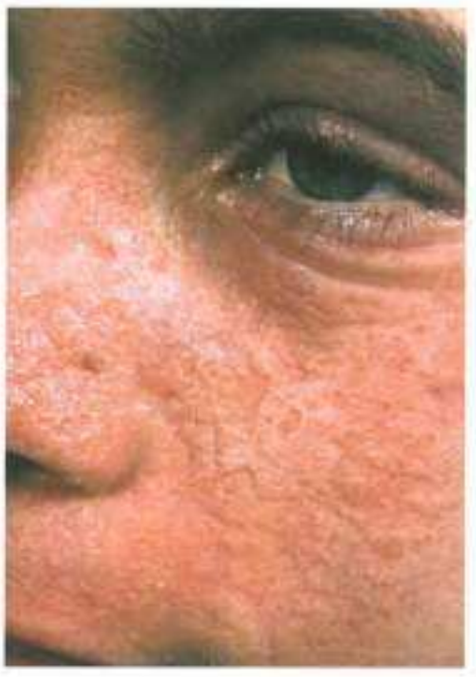


Fig. 22.121 Erythropoietic protoporphyria. Burning and smarting of the skin occurs within minutes of exposure to the sun. Pitted and linear scars may subsequently appear.

Patients with porphyria cutanea tarda have hepatic iron overload; mutations in the gene associated with hereditary haemochromatosis have been associated with both sporadic and acquired porphyria cutanea tarda.

Uroporphyrinogen decarboxylase is defective and both isomers of uroporphyrin accumulate. They are found in excess in the urine and fluoresce red. Coproporphyrins are also increased. The defect is expressed chiefly in the hepatocytes. The more hydrophilic porphyrins released are excreted primarily through the kidneys and, therefore, appear in the urine, while the more hydrophobic ones are excreted in the stool. Skin biopsy typically reveals a cell-free subepidermal blister.

The defective enzyme is located on the short arm of chromosome 1 (1p 34). There are four types of porphyria cutanea tarda, depending on the cellular location of the uroporphyrinogen decarboxylase defect. Type I is acquired and types II and III are inherited and less common.

- **Type I: the sporadic or acquired form** This is the most common (80% of cases). Only the hepatic enzyme is defective and is not sufficient on its own to produce clinical signs but needs a hepatotoxic trigger.
- **Type II** This form is inherited as an autosomal dominant with decreased enzyme activity in all tissues including erythrocytes.
- **Type III** Hepatoerythropoietic porphyria. A rare autosomal recessive form of familial PCT resulting from deficient (but not absent) uroporphyrinogen decarboxylase (UROD), due to a mutation in the UROD gene. There is extreme photosensitivity and skin fragility (which may be misdiagnosed as child abuse) in infancy or early childhood. There is hypertrichosis, erythrodontia, pink urine and sclerodermal changes leading to disfigurement similar to Gunther's disease, but haemolytic anaemia and extracutaneous manifestations are less marked.
- **Type IV** This variety is associated with the hepatotoxicity of hexachlorobenzene.

Clinical Features

Symptoms

Usually starting in adult life, patients observe that their skin is very fragile, breaks at the slightest trauma and blisters in the sun.

Morphology

There are a number of features:

- vesicles or bullae (Fig. 22.122) that break easily, leaving erosions (Figs 22.123 and 22.124) behind that heal with milia formation (Fig. 22.125) and scars
- hypertrichosis, particularly along the temples and cheeks and may be a presenting symptom in women; the children involved in the Turkish epidemic had severe hypertrichosis
- hyperpigmentation (Fig. 22.122) and gross solar elastosis (Fig. 22.126)
- sclerodermatous changes may occur in both light-exposed and light-protected areas, particularly the upper chest.

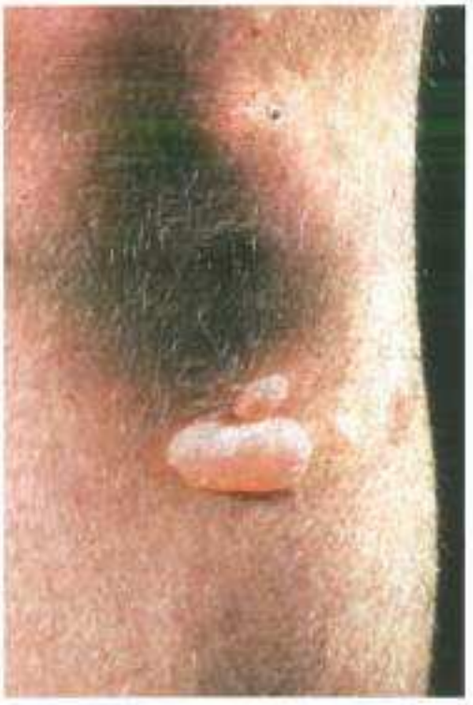


Fig. 22.122 Porphyria cutanea tarda. Skin fragility and blisters followed by erosions are the common complaints. It starts late (tarda) in the acquired form and requires a cofactor (e.g. alcohol) for its expression. Note the pigmentation which frequently accompanies porphyria.

Distribution

The lesions occur on the backs of the hands, the forearms and face.

Systemic signs

Some patients note darkening of the urine. Cirrhosis and hepatocellular carcinoma may develop.

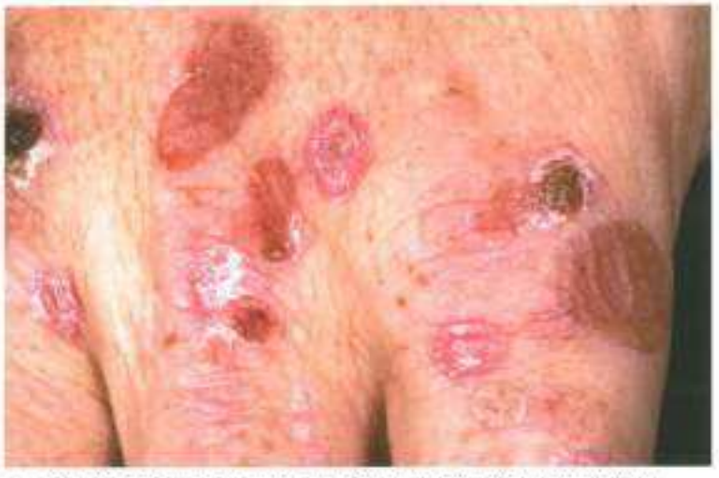


Fig. 22.123 Porphyria cutanea tarda. Fragility of the skin in light-exposed areas, with blisters and erosions, is characteristic.

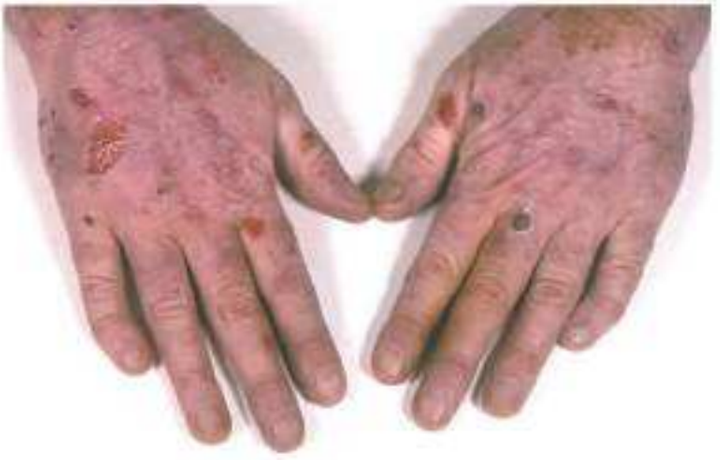


Fig. 22.124 Porphyria cutanea tarda. The sun-exposed areas are most severely affected. The skin is fragile and breaks with the slightest trauma, resulting in erosions and blisters. Note that this patient also has vitiligo.

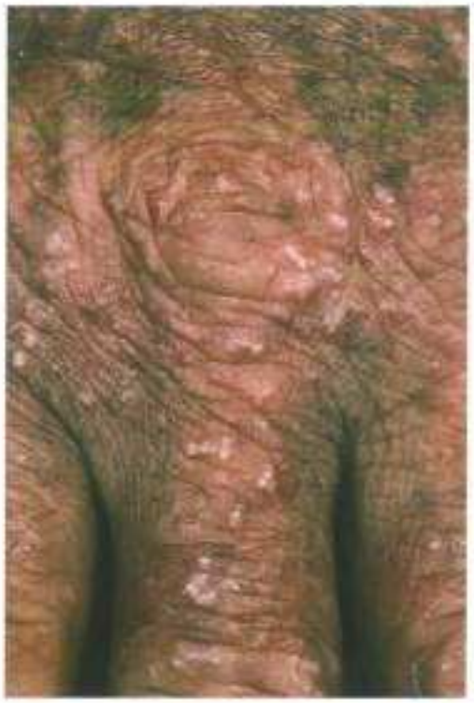


Fig. 22.125 Porphyria cutanea tarda. Small white epidermoid cysts (known as milia) form following damage to the basement membrane at the dermo-epidermal junction from the blistering process. This patient had myelodysplasis syndrome, a rare associated disorder.

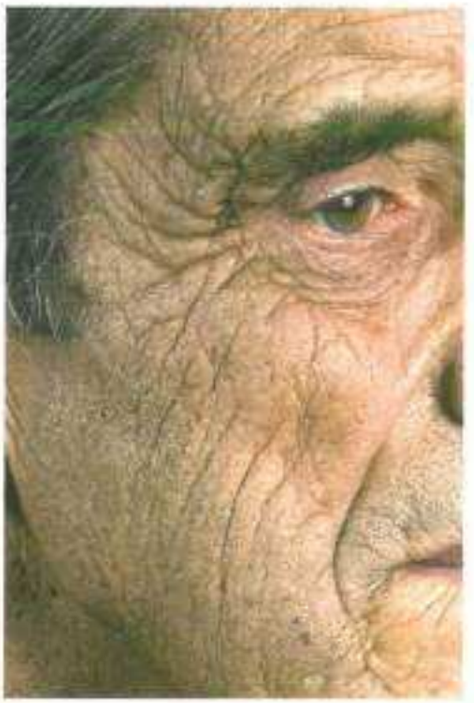


Fig. 22.126 Porphyria cutanea tarda. Hyperpigmentation and gross solar elastosis may accompany the disease.

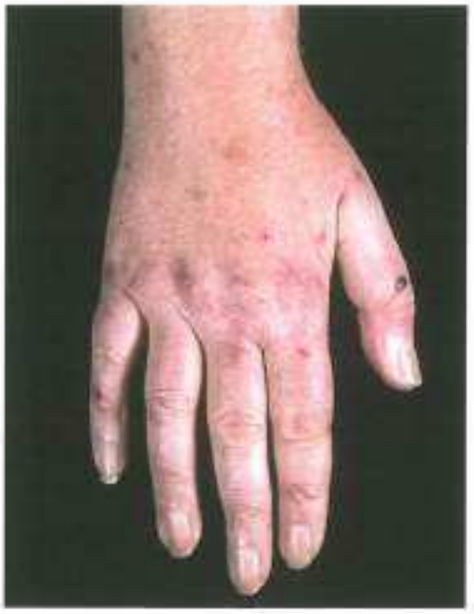


Fig. 22.127 Pseudoporphyria. In patients on chronic ambulatory peritoneal dialysis, cutaneous changes of porphyria cutanea tarda may occur; urinary porphyrins are normal but faecal isocoproporphyrins are raised.

Management

The differential diagnosis is variegate porphyria. The two can be distinguished by the uroporphyrins found in the urine. These usually have a ratio of greater than three for urinary uroporphyrin to coproporphyrin in porphyria cutanea tarda whereas in variegate porphyria the ratio is usually less than 1 and there is also increased excretion of faecal isocoproporphyrin. Any precipitating cofactor (including alcohol and drugs) should be eliminated. Syndromes similar to porphyria cutanea tarda have occasionally been described with hepatic tumours and lupus erythematosus.

Venesection is effective and reduces the iron-associated overload. Low-dose chloroquine phosphate is also helpful. Pseudoporphyria cutanea tarda with normal biochemistry may also be precipitated by drugs such as amiodarone, naproxen, hydrochlorothiazide, etretinate, and by sunbed treatment.

Pseudoporphyria (Fig. 22.127) may occur in patients on dialysis for chronic renal failure. This is clinically and histologically identical to porphyria cutanea tarda, although urinary porphyrins are normal and faecal isocoproporphyrin is elevated. Treatment of the pseudoporphyria associated with chronic renal failure is difficult. Venesection is contraindicated because of the anaemia although epoetin (erythropoietin) may be given to increase the haemoglobin prior to venesection. Antimalarial drugs are not effective because the porphyrins removed from the blood by these drugs are not cleared by the dialysis. Transplantation may be necessary.

VARIEGATE PORPHYRIA

An inherited disorder of protoporphyrinogen oxidase, which results in acute neuropsychiatric and abdominal symptoms and, in some cases, phototoxicity precipitated by certain drugs and toxins.

Aetiology

This autosomal dominant disease can be traced to a Dutch couple who settled in South Africa in the 17th century, where the incidence is now the highest in the world. Variegate porphyria occurs in white and mixed race South Africans whereas porphyria cutanea tarda occurs amongst the black African population, often in association with home-made alcohol and iron ingestion from cooking vessels. Where there has been intermarriage, both disorders may occur within the same family. Protoporphyrinogen oxidase is involved in the penultimate step of haem synthesis and is partially defective. Protoporphyrin and coproporphyrin accumulate in the faeces; during acute attacks, porphobilinogen and aminolaevulinic acid accumulate in the urine, but these return to normal during quiet phases. The skin manifestations are identical to those of porphyria cutanea tarda but variegate porphyria is a distinct entity that does not respond to treatment for porphyria cutanea tarda. It is one of the three autosomal dominant disorders that may result in acute attacks of neuropsychiatric and abdominal episodes which may be life threatening. It needs to be identified because it can be precipitated by drugs or illness, especially infection. The list of drugs is extensive but includes sulphur preparations, griseofulvin, barbiturates, certain anaesthetics and alcohol.

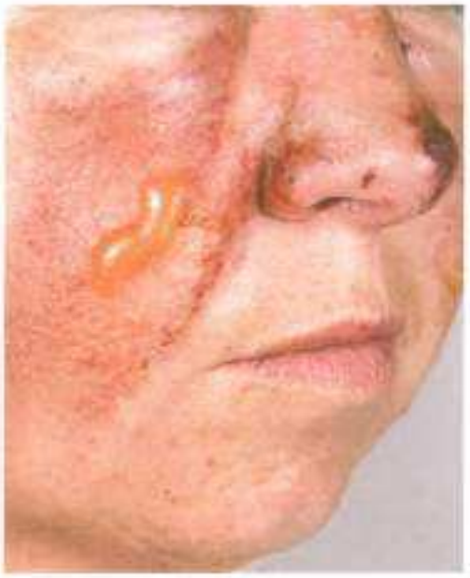


Fig. 22.128 Variegate porphyria. There is acute phototoxicity here. The physical signs are those of porphyria cutanea tarda but acute systemic manifestations occur, as in acute intermittent porphyria, hence the name variegate.

Clinical Features

Symptoms

These develop earlier than in porphyria cutanea tarda after puberty. Patients notice blisters and fragility of the skin, particularly on the backs of the hands.

Morphology and distribution

Photosensitivity (Fig. 22.128) and physical signs are identical to those of porphyria cutanea tarda and hence its name variegate porphyria.

Systemic signs

Acute abdominal crises, CNS abnormalities (including hypomyelination and leukoencephalopathy), peripheral neuropathy and acute psychiatric episodes are features of the acute attacks, just as in acute intermittent porphyria.

Management

The histopathology is of a non-inflammatory subepidermal bulla and thickening of the blood vessel walls (highlighted by PAS) as in porphyria cutanea tarda, and the diagnosis is confirmed by finding elevated levels of protoporphyrin and coproporphyrin in the stools and, in the acute attack, porphobilinogen and aminolaevulinic acid in the urine. In order to prevent acute attacks, the patients must be instructed what drugs or agents to avoid. Total sunblocks and solar protection are necessary to reduce blistering and skin fragility and premature ageing of the skin.

HEREDITARY COPROPORPHYRIA

An autosomal dominant defect in coproporphyrinogen oxidase, which results in intermittent acute episodes induced by drugs and in variable photosensitivity.

Aetiology

Coproporphyrinogen oxidase is defective at step 6 of haem biosynthesis (Table 22.1); coproporphyrin III accumulates in the faeces and is diagnostic. During acute attacks, urinary aminolaevulinic acid and porphobilinogen are raised, as in acute intermittent porphyria and variegate porphyria. It is very rare.

Clinical Features

The photosensitivity and skin lesions are similar to those in porphyria cutanea tarda but only occur in about 30% of patients. The acute episodes are similar to those in acute intermittent porphyria and variegate porphyria.

Management

The diagnosis is confirmed by the biochemical findings and the management is the same as for variegate porphyria.

ACUTE INTERMITTENT PORPHYRIA

Acute intermittent porphyria is an autosomal dominant disorder caused by deficiency of uroporphyrinogen synthetase, which results in acute abdominal, psychiatric and CNS symptoms, usually precipitated by drugs or infection.

Aetiology

The enzyme uroporphyrinogen I synthetase (also called porphobilinogen deaminase) is partially deficient at step 3 of haem biosynthesis (Table 22.1), which results in accumulation of porphobilinogen and aminolaevulinic acid. This is the third variety of porphyria that may have acute episodes precipitated by drugs or other agents. Not all carriers (probably less than 10%) of the disease have symptoms but all do excrete porphobilinogen and aminolaevulinic acid in the urine, even between attacks.

Clinical Features

Porphobilinogen and aminolaevulinic acid are not photoactive so there are no cutaneous signs in the disease.

Systemic signs

The abdominal pain in acute attacks is severe. Constipation is usual. Neurological symptoms include paralysis and mental disturbance.

Management

The diagnosis is made biochemically and the management is the same as that for variegate porphyria. It is important in all these varieties of porphyria to check relatives, even if they are asymptomatic, for the presence of the disease.

Disorders of joints

Several rheumatological conditions are associated with cutaneous abnormalities. The classic examples are psoriasis and Reiter's syndrome (Ch. 5). Gout is a hyperuricaemic condition that may result in deposits of urates, especially in the skin and cartilage of the pinna of the ear (Fig. 22.129) and around the joints (Fig. 22.130). They are known as tophi, have a light pink colour and occasionally drain a white material that contains urate crystals. The cutaneous abnormalities associated with rheumatoid arthritis and Behçet's syndrome are described here.

RHEUMATOID ARTHRITIS

The cutaneous changes may include:

- **Rheumatoid nodules**. These are firm subcutaneous nodules that occur in about 20% of patients with severe rheumatoid arthritis; they occur particularly along the ulnar border of the forearms, on the backs of the hands (Fig. 22.131) and on the knees. The rheumatoid and antinuclear factors are usually positive. If the nodules ulcerate, particularly on areas subject to pressure, secondary infection, septicaemia and septic arthritis may result.

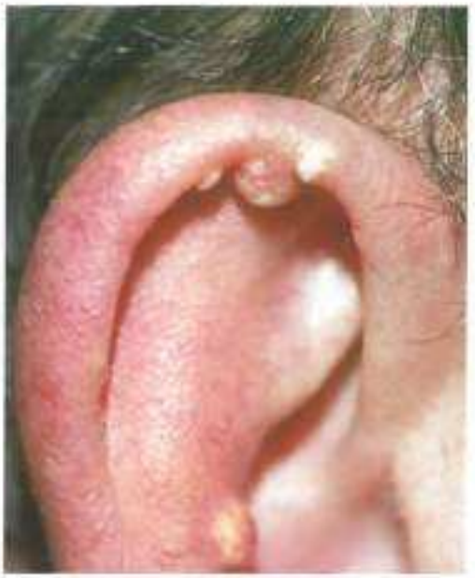


Fig. 22.129 Gouty tophi. Deposits of urate occur as hard papules around the pinnae.

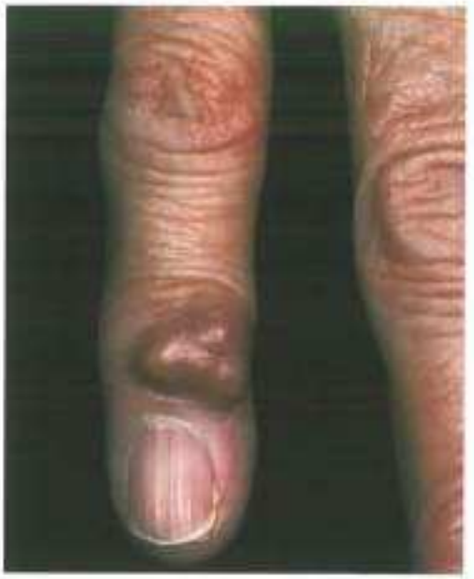


Fig. 22.130 Gouty tophus. Deposits of urates (known as tophi) may be found around the joints. They occasionally drain a white material containing urate crystals.

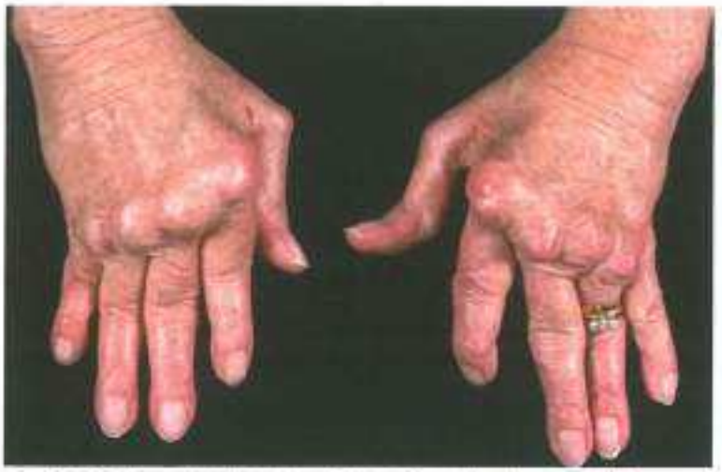


Fig. 22.131 Rheumatoid nodules. These are firm subcutaneous nodules, seen here over the metacarpal phalangeal joints in association with the destructive changes of rheumatoid arthritis.

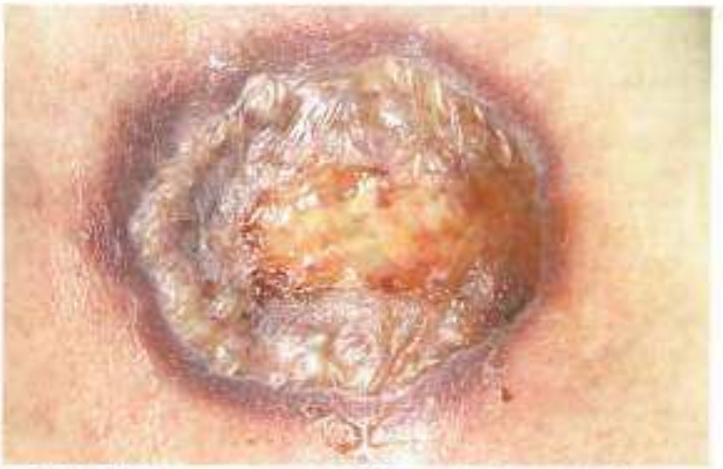


Fig. 22.132 Pyoderma gangrenosum. This occurs in rheumatoid arthritis as well as other disorders. Note the purple margin surrounding the central ulceration and vesiculo-bullous periphery.

- **Vascular lesions** Small, painless, red-brown infarcts in the region of the nailfolds or larger painful haemorrhagic maculopapular lesions on the pads of the fingers are caused by small-vessel vasculitis (Bywater's lesions). They last 2 or 3 days. They are not specific to rheumatoid arthritis but they are very characteristic.
- **Necrotizing vasculitis** A vasculitis, similar to that of polyarteritis nodosa, may be associated with rheumatoid arthritis. There is often widespread polyneuropathy and systemic involvement and it carries a grave prognosis.
- **Livedo reticularis**
- **Leg ulcers** Gravitational ulcers are common and difficult to treat because patients have difficulty applying bandages. They result from an inactive muscle pump. Leg ulcers may also result from vasculitis or from pyoderma gangrenosum.
- **Annular erythema** This may occur in Still's disease. It consists of small, asymptomatic, pink macules or papules with an irregular margin. Larger lesions up to a few centimetres in size show a central pallor. The colour is characteristically described as salmon-pink; the lesions occur most often on the limbs and trunk, last only a few hours and are particularly present in the middle of the day or in the evening, especially if the patient has a temperature. Annular erythema does occur very rarely in seropositive adults.
- **Pressure sores**
- **Pyoderma gangrenosum** (Fig. 22.132) Also occurs in other diseases such as inflammatory bowel disease and myeloma.
- **Rheumatoid neutrophilic dermatitis** This eruption is composed of non-tender, urticarial or annular erythematous subcutaneous papules, plaques or nodules, which last for up to 3 weeks. They have a distinctive histology of a dense infiltrate of neutrophils involving the dermis and often the subcutaneous fat and resemble other neutrophilic vascular dermatoses such as Sweet's syndrome, pyoderma gangrenosum and the pustular vasculitis of Behçet's syndrome.

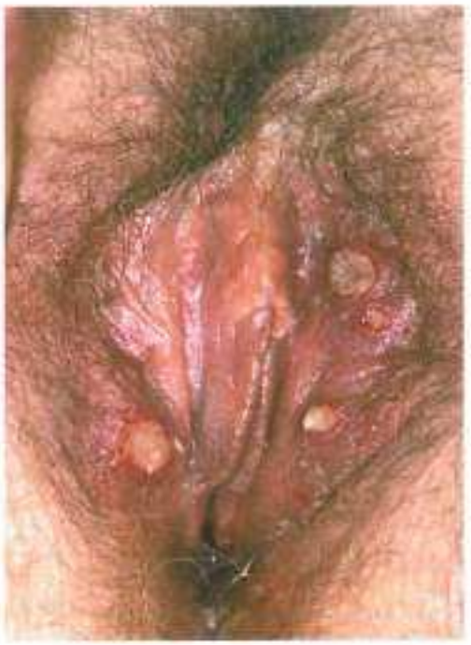


Fig. 22.133 Behçet's syndrome. The labia are affected, often with multiple ulcers of varying size, and this may suggest the diagnosis.

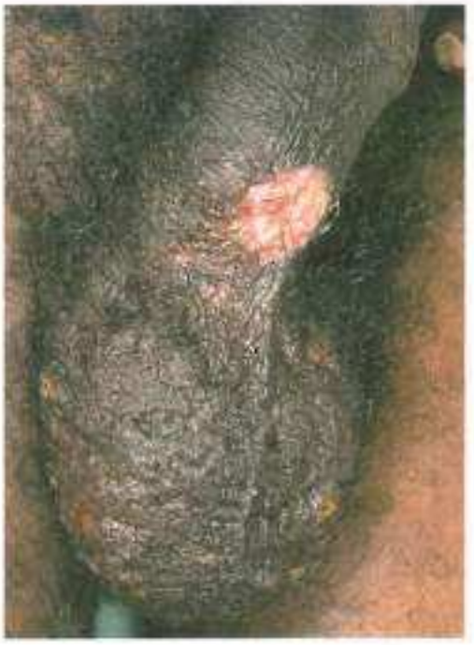


Fig. 22.134 Behçet's syndrome. The root of the penis has a large ulcer with a yellow base. The condition is more common in males, in the Middle East and Japan and in early adult life.

- **Palisaded neutrophilic and granulomatous dermatitis** A pathological reaction pattern with a wide range of clinical features including papules on extensor surfaces especially elbows and fingers (may have central umbilication-like papular granuloma annulare), annular plaques and linear, often burning cordlike lesions on the lateral trunk and skin folds. It is probably a subacute or chronic smouldering small vessel vasculitis secondary to immune complexes from the underlying connective tissue disorder, causing degeneration of collagen and inciting a lymphohistiocytic palisading reaction rather than acute necrosis.
- **Transparent skin, palmar erythema, urticaria and vitiligo** These are less common changes.

BEHÇET'S SYNDROME

A chronic multisystem disease characterized by recurrent oral and genital ulceration, arthritis and uveitis.

Aetiology

The disorder is common in the Middle East and Japan and along the old silk route. There is a significant association with HLA-B5 (ocular) and B12 (mucocutaneous). The mean onset is in early adult life. It is rare in children, the elderly and blacks. The finding of a leucocytoclastic vasculitis or a lesser degree of a neutrophilic vascular reaction including Sweet's syndrome is suggestive that this is an immune complex disorder, possibly mediated by an infectious agent such as herpes simplex and/or streptococci, with immune dysregulation and inflammatory mediators. It is sometimes associated with thrombosis as part of a prothrombotic or hypercoagulable state.

Clinical Features

Symptoms

The ulcers are painful.

Morphology and distribution

- **Oral and genital ulcers** The oral lesions are similar to aphthous ulcers. They may be single or, more often, multiple, small or quite large. They persist for at least 2 weeks and frequently longer. They have a yellow base with a red margin. Similar lesions occur on the genitalia, especially the scrotum, labia (Fig. 22.133) and around the root of the penis (Fig. 22.134). Patients have at least three outbreaks a year.
- **Erythema nodosum**
- **Papular pustular lesions** (Fig. 22.135), **folliculitis and acne** Pustular lesions (Fig. 22.136) may also occur at the sites of trauma, including needle punctures, (a phenomenon known as pathergy).
- **Pyoderma gangrenosum**
- **Cutaneous vasculitis**
- **Sweet's syndrome** (Ch. 18)

Systemic signs

The white count, ESR, immunoglobulins and C reactive protein may be raised during exacerbations.

The eye changes are of posterior uveitis (which is the most common cause of blindness because of arterial and venous occlusion), conjunctivitis, hypopyon (Fig. 22.137), corneal ulceration, papilloedema and arteritis. The arthritis is non-erosive, inflammatory and oligoarticular, usually affecting the knees and ankles. There are many neurological manifestations, including headaches, meningoencephalitis, seizures, central venous thrombosis, cranial nerve palsy, cerebellar ataxia, hemiplegia and benign intracranial hypertension. There may be ulceration along the gastrointestinal tract leading to symptoms of diarrhoea and bloating particularly in the Japanese, which is rare elsewhere. The lungs, cardiovascular system and renal tract are occasionally involved.

Management

The diagnosis is a clinical one because there is no specific test, although a skin biopsy 48 hours after injection of histamine may show a vasculitis (a manifestation of pathergy). *Aphthous ulcers* (Fig. 22.138) are common but genital ulceration is suggestive. In *complex aphthosis*, the ulcers are usually constant. More than three are present at any time and there are no systemic manifestations. The onset is in childhood or adolescence and gets less severe with advancing age. There may be associated deficiencies of vitamin B complex, folate, iron and zinc, with a response to replacement therapy. Patients may also have cyclical neutropenia, agranulocytosis or myelodysplastic syndrome.

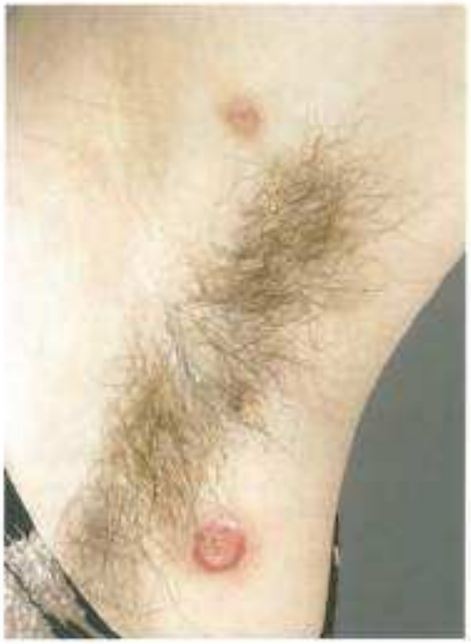


Fig. 22.135 Behçet's syndrome. Sterile folliculitis or pyodermas are common on the skin.

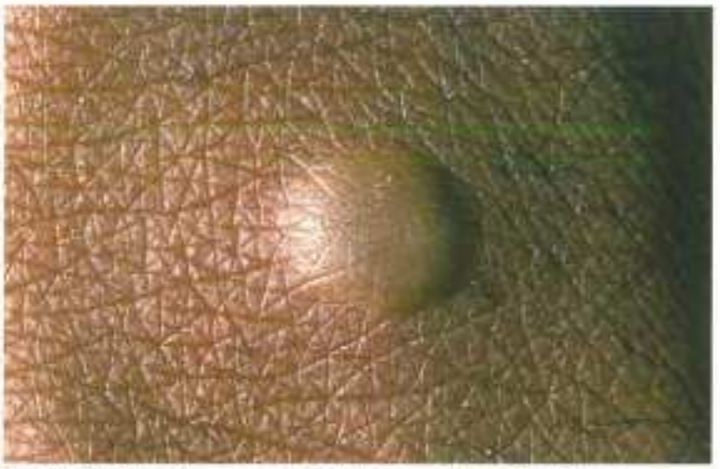


Fig. 22.136 Behçet's syndrome. Pustules may occur at sites of trauma (including venepuncture sites), a phenomenon known as pathergy.

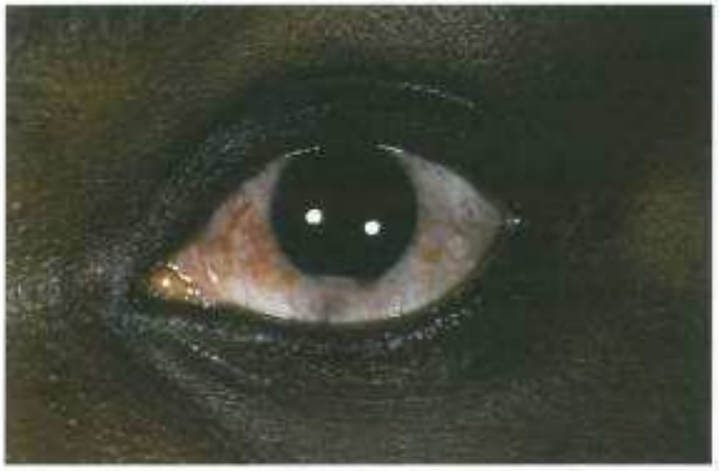


Fig. 22.137 Behçet's syndrome. Hypopyon is present. Other ocular abnormalities including posterior uveitis are common.

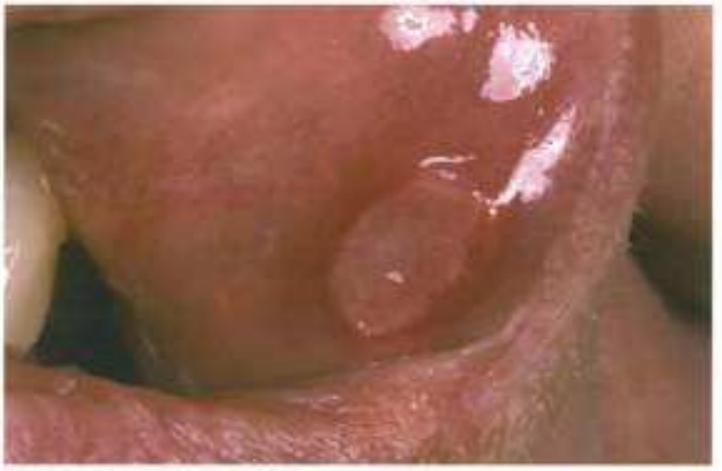


Fig. 22.138 Behçet's syndrome. The ulcers have a yellow base with red margin similar to aphthous ulcers but may be larger and more persistent.

The ocular lesions, arthritis, neurological involvement and the peculiar pustular lesions may suggest the diagnosis. Treatment is unsatisfactory. Topical or intralesional steroids and tetracycline mouthwashes may help the ulceration. Thalidomide 100 mg or more per day may be tried in severe disease but it is a teratogen and neurotoxic. Dapsone is used for its anti-neutrophilic effects. Colchicine also inhibits neutrophil migration and phagocytosis. Low-dose methotrexate plus interferon alfa, cyclophosphamide, ciclosporin, azathioprine and minocycline have also been used. The prognosis is related to the CNS and pulmonary involvement. Bowel perforation may be a cause of death.

Disorders of the gastrointestinal tract

LIVER DISEASE

Certain disorders affecting the liver may have cutaneous complications:

- **Infections** A transient prodromal serum sickness-like syndrome occurs in about a third of patients with acute hepatitis B infection. Urticaria, and in some cases a leucocytoclastic vasculitis is present in the pre-icteric stages. Hepatitis B infection has also been associated with cryoglobulinaemia, polyarteritis nodosa and the Gianotti–Crosti syndrome. Hepatitis C has been associated with porphyria cutanea tarda and immune complex vasculitis, particularly cryoglobulinaemia but also polyarteritis nodosa and mucocutaneous lichen planus.
- **Chronic active hepatitis** Acne, lupus erythematosus-like eruptions or localized scleroderma may be present.

- **Haemochromatosis** A metallic grey or brown hyperpigmentation occurs in this disorder of iron overload that leads to cirrhosis and diabetes mellitus. The pigmentation appears to be caused, however, by melanin and not iron and is most pronounced in sun-exposed areas, in the palmar creases and areolae. Freckles may be prominent.
- **Primary biliary cirrhosis** Hyperpigmentation (Fig. 22.139), pruritus, xanthomas, lichen planus, scleroderma and vitiligo (Fig. 22.140) may occur.
- **Wilson's disease** Pretibial hyperpigmentation may be present.
- **Alcoholic liver disease** Psoriasis is five times more common. Scurvy may occur owing to poor diet.

The cutaneous signs of liver disease include jaundice (Fig. 22.141), spider naevi (Fig. 22.142), palmar erythema (Fig. 22.143), diffuse scattered telangiectatic vessels, purpura, loss of body hair (Fig. 22.144) and nail changes (including clubbing and Terry's nails). Generalized pruritus is associated with obstructive forms of liver disease and is frequently the presenting complaint in primary biliary cirrhosis.

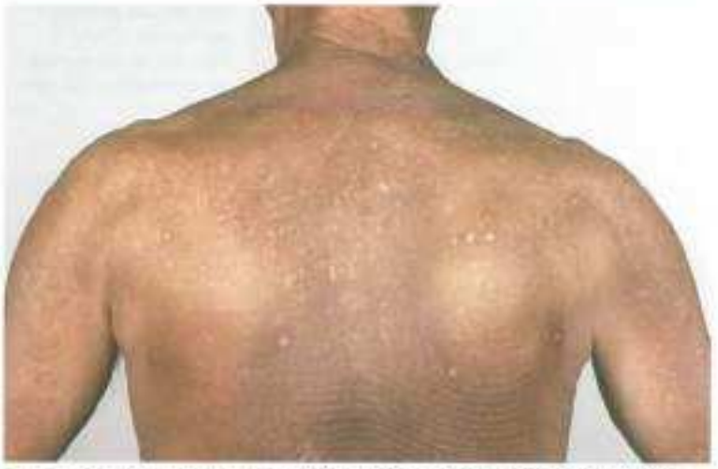


Fig. 22.139 Hyperpigmentation. Gradual deepening of the colour of the skin and failure of a suntan to fade may be the presentation of primary biliary cirrhosis. Note the scars from scratching.

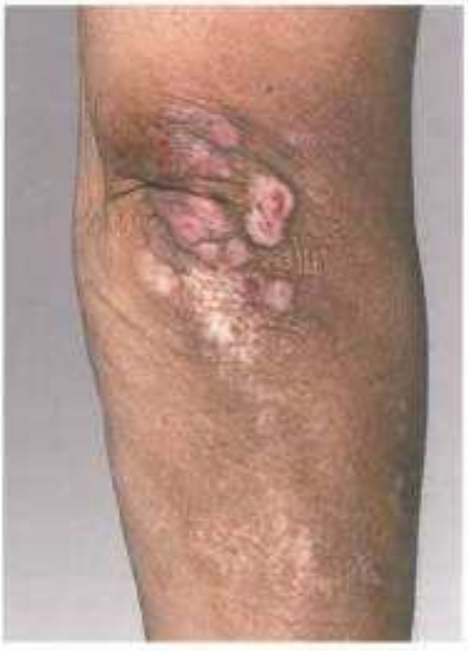


Fig. 22.140 Vitiligo, prurigo and primary biliary cirrhosis. This woman had vitiligo, noticed her skin was darkening and complained of generalized itching, which has led to excoriated nodules.

Fig. 22.141 Jaundice. The skin and conjunctivae become yellow. Pruritus occurs in obstructive forms. Excoriations (scratch marks) are prominent on his forehead.

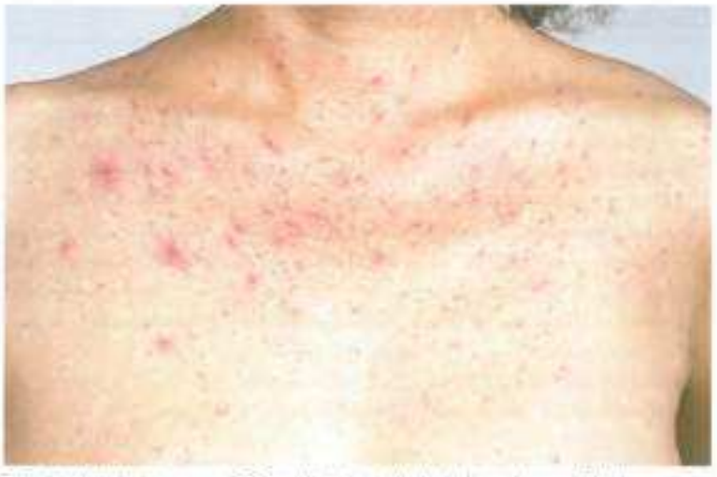


Fig. 22.142 Spider naevi. This patient had alcoholic liver disease. She is jaundiced and there are multiple spider naevi.

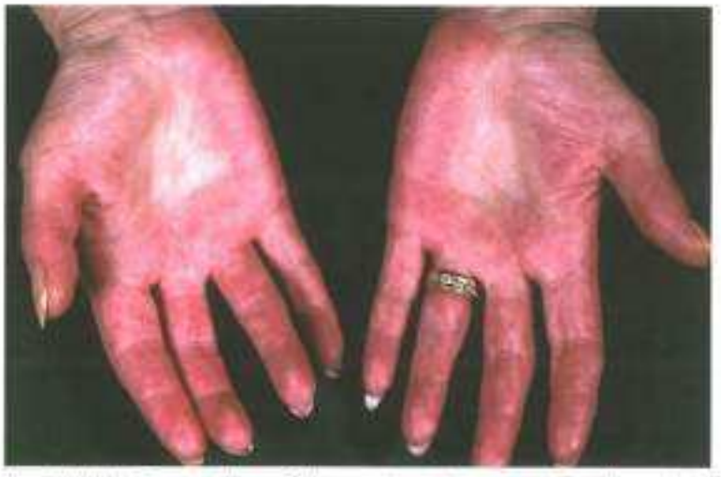


Fig. 22.143 Palmar erythema. Palmar erythema is common in liver disease but may also occur in pregnancy and rheumatoid arthritis.

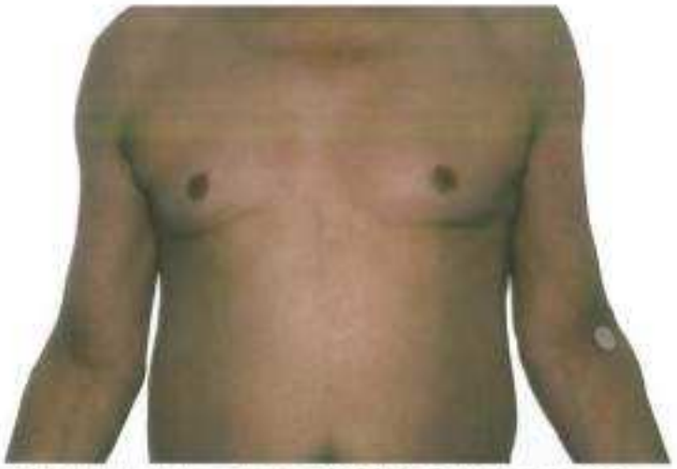


Fig. 22.144 Alcoholic liver disease. Loss of body hair and gynaecomastia occur as a result of failure of the liver to metabolize circulating hormones.

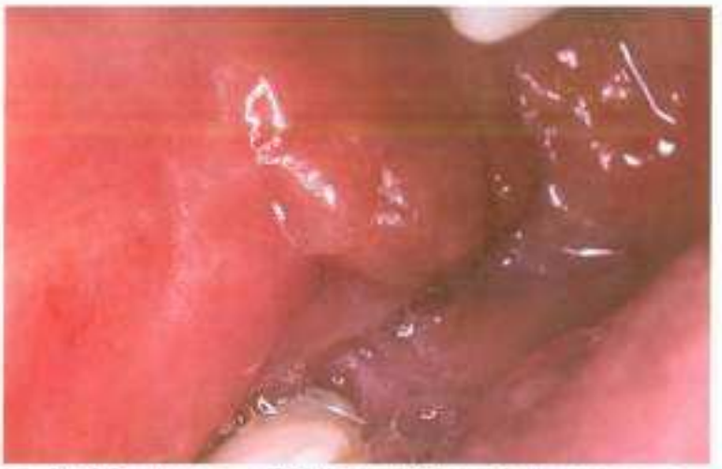


Fig. 22.145 Crohn's disease. Thickening and folding of the mucosae occur in primary Crohn's disease, producing tags and a cobblestone effect.

Fig. 22.146 Crohn's disease. Both upper and lower lips are swollen and fissured. There may be thickening and folding of the mucosae producing a cobblestone appearance. Biopsy shows non-caseating granuloma and lymphoedema.

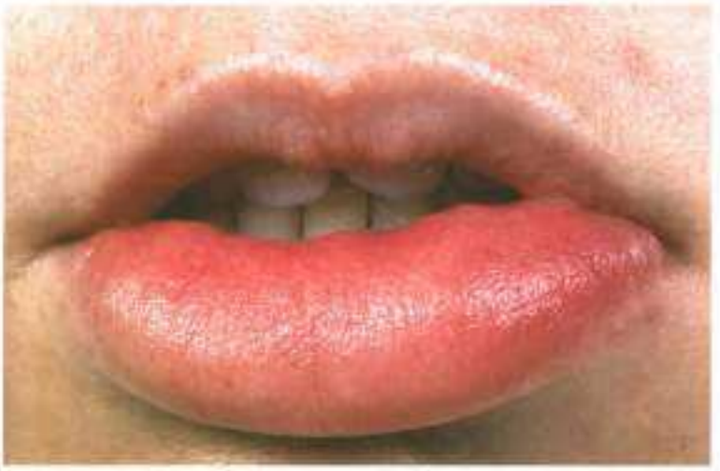


Fig. 22.147 Melkersson–Rosenthal syndrome. A granulomatous cheilitis of the lower lip may occur in association with recurrent facial palsy and a scrotal tongue.

DISORDERS OF THE BOWEL

Inherited disorders Those which may affect the bowel and have cutaneous signs include:

- **Hereditary haemorrhagic telangiectasia** (Ch. 20)
- **Pseudoxanthoma elasticum** (Ch. 20)
- **Ehlers–Danlos syndrome** (Ch. 20)
- **Gardner's, Muir–Torre, Cowden's** (Ch. 9) and **Peutz–Jeghers' syndromes** (Ch. 20)
- **Howel–Evans' syndrome** This is familial tylosis associated with oesophageal carcinoma and leukoplakia. (Sporadic tylosis may be associated with carcinoma of the lung and oesophagus).

Inflammatory bowel disease Aphthous ulceration, pyoderma gangrenosum, erythema nodosum and cutaneous vasculitis may occur. In Crohn's disease, there may be contiguous extension of the intestinal disease to give rise to abscesses and fistulae in the perineal area, sinuses in the abdominal wall or groins and non-contiguous, non-caseating granulomatous genital lymphoedema and involvement of the mouth (Fig. 22.145). The last (Fig. 22.146) is similar to the granulomatous cheilitis (Fig. 22.147) of the *Melkersson–Rosenthal syndrome*, which is associated with recurrent facial palsy and scrotal tongue. Coeliac disease is associated with dermatitis herpetiformis.

Fig. 22.148 Anorexia nervosa.
This 33-year-old is severely undernourished. Superficial epidermal necrosis occurs with desquamation and hyperpigmentation. Skin biopsy shows epidermal vacuolation and atrophy. Deficiency of zinc and other minerals are responsible.

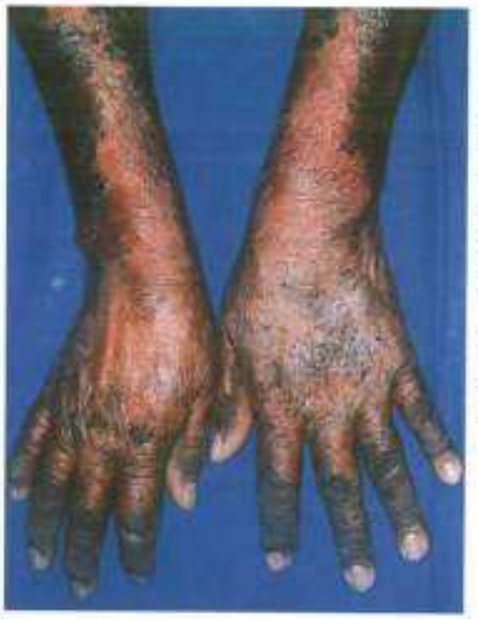


Fig. 22.149 Pellagra.
This is a triad of a photosensitive dermatitis, diarrhoea and sometimes dementia that occurs secondary to tryptophan deficiency often due to malnutrition. Here there is hyperpigmentation and desquamation following erythema in a light-exposed distribution. (With permission from Bolognia JL, Jorizzo JL, Rapini RP, et al: Dermatology, 2nd edition. London: Elsevier, 2008.)

Nutritional disorders Those associated with malabsorption (e.g. acrodermatitis enteropathica – see below) or poor diet (e.g. anorexia nervosa, Fig. 22.148) may give rise to specific conditions.

- **Pellagra** A triad of a photosensitive dermatitis (Fig. 22.149), diarrhoea and dementia. It results from vitamin B_3 deficiency (niacin and nicotinic acid, which are present in liver, poultry, salmon, pork and red meat). It is formed from the essential fatty acid tryptophan in the liver. It is caused by poor diet, malabsorption or abnormal tryptophan metabolism (as in carcinoid syndrome, Hartnup disease or chemotherapy with isoniazid, 6-mercaptopurine, chloramphenicol or 5-fluorouracil), or corn-rich diet.
- **Scurvy** A dietary disorder resulting from low levels of vitamin C (ascorbic acid) as a result of malnutrition, anorexia nervosa or alcoholic liver disease. Humans cannot synthesize vitamin C and body stores are depleted within one to three months. It is a necessary cofactor for collagen biosynthesis. Deficiency leads to corkscrew hairs, perifollicular petechiae (Fig. 22.150), ecchymoses and hyperkeratosis. There is gingival haemorrhage and swelling, perlèche of the lips and sides of the nose and erythema and scaling of the soles. Bone disease results from subperiosteal bleeding. 1 g ascorbic acid daily stops gingival bleeding within 24 hours and corrects the anaemia within a month.

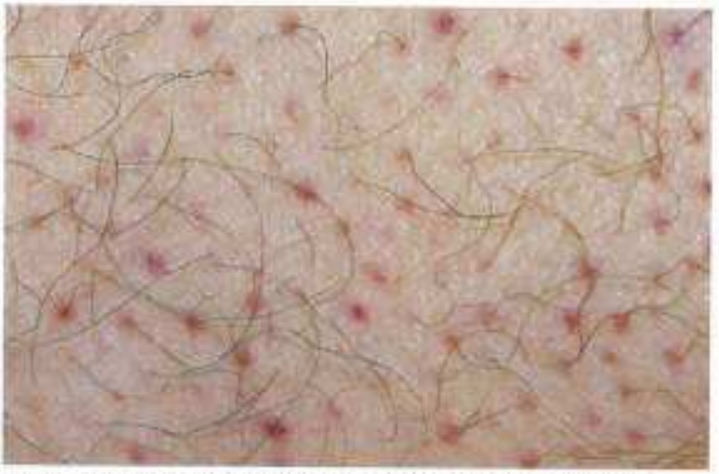


Fig. 22.150 Scurvy. There are perifollicular petechiae and corkscrew hairs resulting form vitamin C deficiency. More widespread bleeding (ecchymoses) and hyperkeratosis also occurs. (Courtesy of Dr Emma Craythorne.)

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is a triad of circumorificial and acral dermatitis, alopecia and diarrhoea associated with zinc deficiency.

Aetiology

Zinc is an essential trace element in the diet, particularly meat. It is absorbed through the proximal small bowel and excreted in the stool. Acrodermatitis enteropathica is a rare autosomal recessive disorder presenting in infancy that was frequently fatal although some cases were ameliorated by diiodohydroxyquin. Since Moynahan and Barnes discovered that zinc replacement dramatically improved the wellbeing of these children, acrodermatitis enteropathica is used to describe any disorder secondary to zinc deficiency. Causes include plants and high-fibre diets that contain phytate, which may complex with zinc and reduce its bioavailability, inadequate zinc intake (from anorexia nervosa, vegetarian diets or parenteral alimentation) and reduced zinc absorption (in coeliac disease, pancreatic insufficiency, cystic fibrosis, severe infantile diarrhoea and alcoholism).

Clinical Features

Symptoms

It presents within a few days or weeks of life, particularly after weaning (colostrum has a much higher zinc content than cow's milk). The child is miserable and unwell. There is failure to thrive and diarrhoea, with malodorous pale and bulky stools.

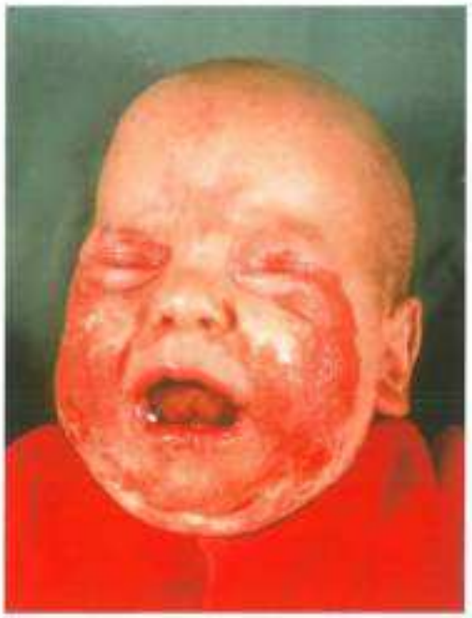


Fig. 22.151 Acrodermatitis enteropathica. There is a symmetrical, oozing, raw eruption around the eyes, mouth, cheek and ears.

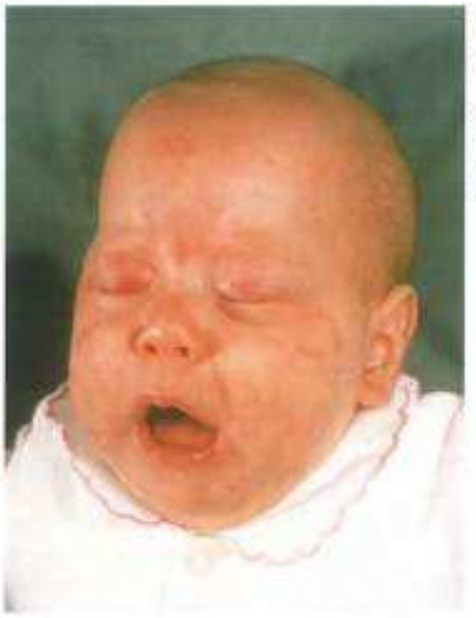
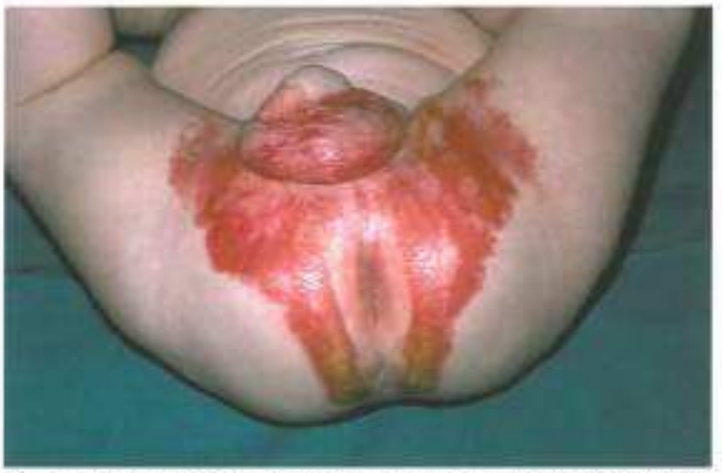
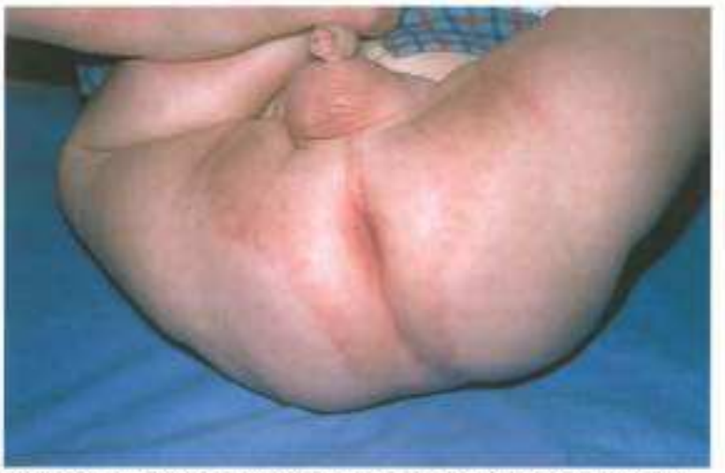


Fig. 22.152 Acrodermatitis enteropathica. The infant is shown 2 weeks after treatment with zinc sulphate. (Courtesy of Dr A. C. Pemproke.)





Figs 22.153 and 22.154 Acrodermatitis enteropathica. Failure to thrive, diarrhoea with malodorous pale and bulky stools and a perioriticial vesiculo-bullous, eroded and crusted rash occurs (Fig. 22.153). It responds to zinc replacement (Fig. 22.154). (Courtesy of Dr Michèle Clement.)

Morphology

It starts as a perlèche (an angular cheilitis at the corners of the mouth) and becomes a vesiculo-bullous eruption that crusts and erodes.

Distribution

The eruptions occur around the orifices (Figs 22.151 and 22.152), particularly the eyes, mouth, ears, nose, anus and genitalia. Similar lesions occur around the finger- and toenails. Psoriasiform plaques may appear on the elbows, knees and buttocks. Secondary invasion of the skin by *Candida albicans* is common. Alopecia is common.

Systemic signs

Anorexia, diarrhoea, mental disturbance, growth retardation, delayed puberty, hypogonadism, photophobia and delayed wound healing are other manifestations.

Management of Acrodermatitis Enteropathica

Zinc may be measured in plasma, serum or urine. The histology shows acanthosis, dyskeratosis, subcorneal pustules and vacuolar abnormalities at the dermo-epidermal junction. Zinc replacement reverses all the effects of the condition (Figs 22.153 and 22.154). The differential diagnosis includes *deficiency of biotinidase*, an enzyme which releases biotin (a key factor for four classes of carboxylases which are required by leucocytes and fibroblasts) from biocytin. The clinical features of the juvenile form are alopecia, perioriticial erythema, onychoschizia, hypotonia, lethargy, seizures, developmental delay, deafness and poor vision. In adults there may be depression in addition to the ectodermal changes and it occurs in parenteral nutrition without biotin, severe malabsorption, food faddists (excessive intake of raw eggs) and those on chronic anticonvulsant therapy.

PANCREATIC DISORDERS

- **Acute pancreatitis** There may be a faint blue discoloration around the umbilicus (Cullen's sign) secondary to a haemoperitoneum and a bruise-like discoloration (Fig. 22.155) of the flanks (*Grey–Turner's sign*) secondary to breakdown of haemoglobin.
- **Panniculitis** (Ch. 18)
- **Cystic fibrosis** A widespread papulo-squamous desquamating rash with periorificial accentuation reminiscent of acrodermatitis enteropathica may occur.
- **Glucagonoma** A necrolytic migratory erythema (see below).

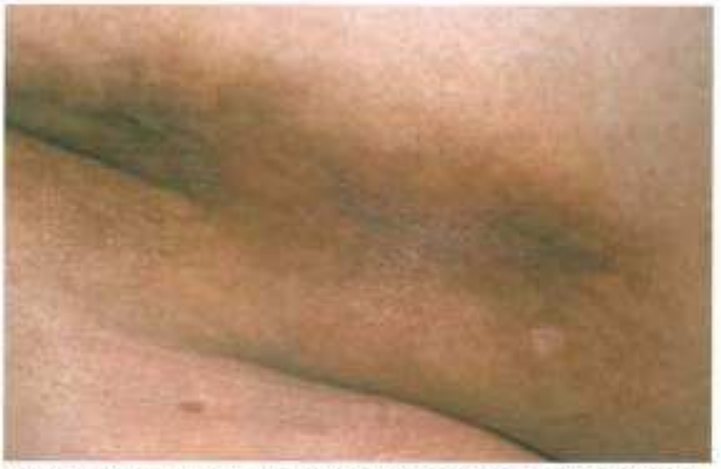


Fig. 22.155 Grey–Turner's sign. A bruise-like discoloration of the flanks occurs as a result of haemoperitoneum in acute pancreatitis.

Renal insufficiency

Renal insufficiency may lead to cutaneous complications either as a result of poor kidney function, treatment, or genetic or acquired diseases. Generalized pruritus, xerosis, increased pigmentation, poor wound healing, purpura and half and half nails are common.

- **Pseudoporphyria cutanea tarda** This (Figs 22.127 and 22.156) may occur during haemo- but not peritoneal dialysis, possibly caused by photosensitizing chemicals being leached from the polyvinyl chloride dialysis tubing (not used in peritoneal dialysis), or possibly the aluminium hydroxide in the dialysate, which can cause similar changes in rats.
- **Scleroderma (gadolinium nephrogenic systemic fibrosis)** (Ch. 21).
- **Infection** Warts, extensive dermatophytosis and opportunistic infections (e.g. alterneria alternata) result from immunosuppression following transplantation.
- **Acquired perforating folliculitis** Occurs in 5 to 10% of patients with haemodialysis. It is also seen in diabetes mellitus (Ch. 20).
- **Cutaneous malignancy** Immunosuppression following renal transplantation leads to a greatly increased risk of squamous cell carcinoma with an 8% mortality and Kaposi's sarcoma (Ch. 14).
- **Disorders that affect the skin and the renal tract** These include Henoch–Schönlein purpura, collagen vascular diseases, polyarteritis nodosa, Wegener's granulomatosis and amyloidosis.
- **Lipodystrophy** A partial lipodystrophy (Fig. 22.157) is associated with a membranous glomerulonephritis and circulating C3 nephritic factor.
- **Hereditary renal cutaneous syndromes** These include angiokeratoma corporis diffusum, neurofibromatosis (outflow obstruction from the neurofibroma, renal artery stenosis, phaeochromocytoma or nephroblastoma), tuberous sclerosis (rhabdomyoma and carcinoma), nail patella syndrome (glomerulonephritis) and von Hippel–Lindau syndrome (renal cysts or adenocarcinoma).
- **Metastatic cutaneous calcification** This can result from elevated calcium or phosphate levels in chronic renal failure, secondary to poor renal clearance of phosphate, leading to increased parathormone levels, hypercalcaemia and hyperphosphataemia. Benign nodular calcification

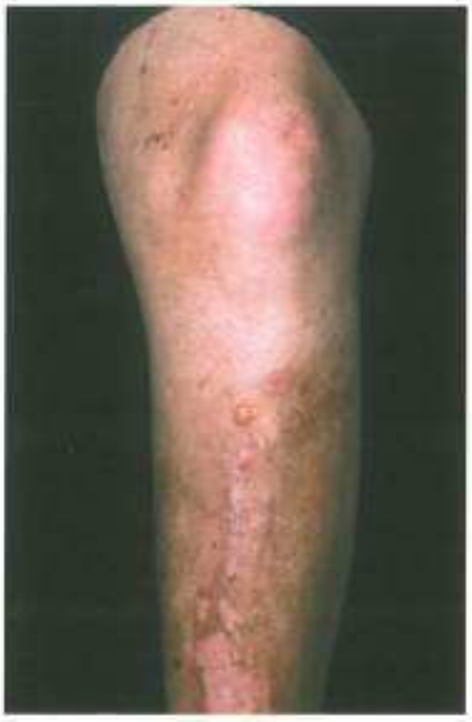


Fig. 22.156 Pseudoporphyria cutanea tarda. There is fragility of the skin such that blistering occurs with the most minor trauma. Scarring and sclerodermatous changes result. This man was a diabetic on haemodialysis for renal insufficiency.

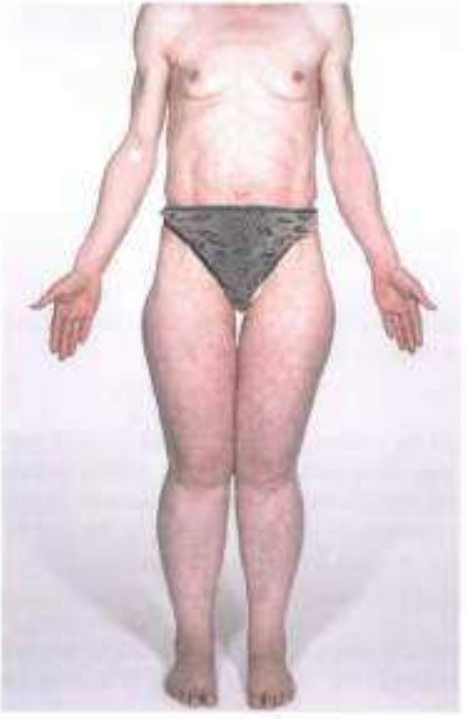


Fig. 22.157 Partial lipodystrophy. There is loss of fat in the upper half of the body, often with hypertrophy in the lower half, most commonly in women associated with a progressive membranous mesangiocapillary glomerulonephritis.

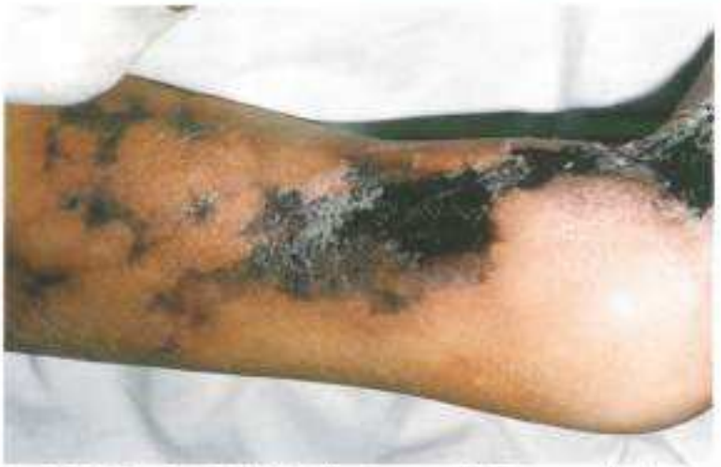


Fig. 22.158 Calciphylaxis. Metastatic cutaneous calcification occurs in chronic renal failure. There is painful violaceous mottled livedo patterning with ulceration. (Courtesy of Dr Elissbeth Higgins.)

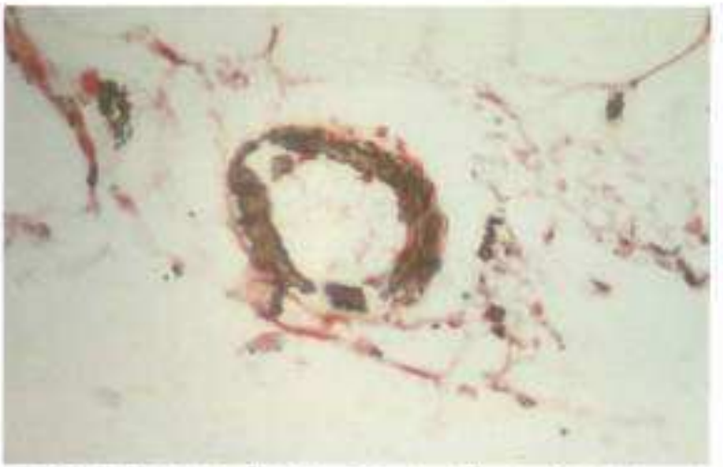


Fig. 22.159 Calciphylaxis. Histologically, there is calcification of the blood vessel walls. (Courtesy of Dr E. Higgins.)

or fatal calciphylaxis may occur. Other causes of metastatic calcification include hyperparathyroidism, both primary and secondary, the milk alkali syndrome, hypervitaminosis D, AIDS, sarcoidosis and myeloma.

- **Calciphylaxis** This is a commonly fatal vasculopathic disorder characterized by cutaneous ischaemia and necrosis (Fig. 22.158), which occurs when calcium salts are deposited in the microvasculature (Fig. 22.159) and cause thrombosis of the pannicular arteries. Clinically, there is a reticulate purpura and painful ulceration of the breast, buttocks or extremities. There is usually secondary hyperparathyroidism and chronic renal function (occasionally these are normal) and diabetes. Intravenous sodium thiosulphate infusions liberate calcium ions from calcium salt deposits by forming soluble calcium thiosulphate and may facilitate excretion or dialysis of calcium thiosulphate.

Disorders associated with malignant disease

These may conveniently be grouped into four types.

1. **Familial cancer syndromes** with a cutaneous component. These include Cowden's, Muir–Torre, Gardner's, Peutz–Jegher, Birt–Hogg–Dubé, Howel–Evans, Bloom's, Rothmund–Thomson, Gorlin–Goltz syndromes, ataxia telangiectasia, dyskeratosis congenita, xeroderma pigmentosum and neurofibromatosis.
2. **Carcinogens** which produce cutaneous signs and may also cause internal malignancy. The classical example of this is arsenic, which is known to produce pigmentation, keratoses and superficial basal cell carcinomas of the skin and to cause particularly carcinoma of the bronchus.
3. **Secondary deposits** (Figs 22.160 and 22.161), localized spread of the

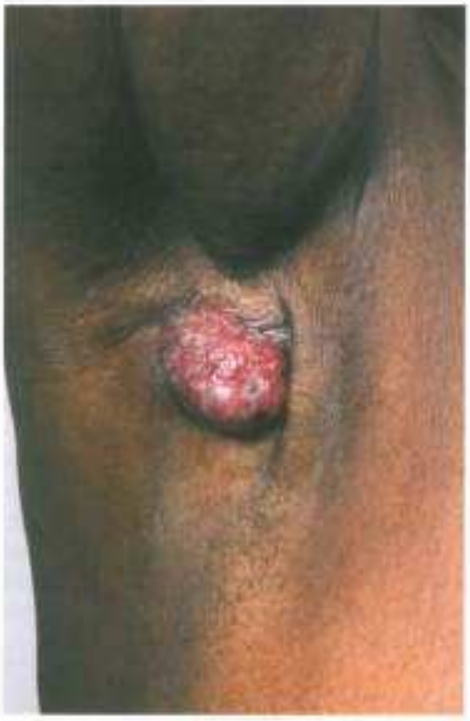


Fig. 22.160 Secondary metastatic deposit. This was from an adenocarcinoma in the colon. The head and trunk are the commonest sites, but metastases may occur anywhere in the skin.

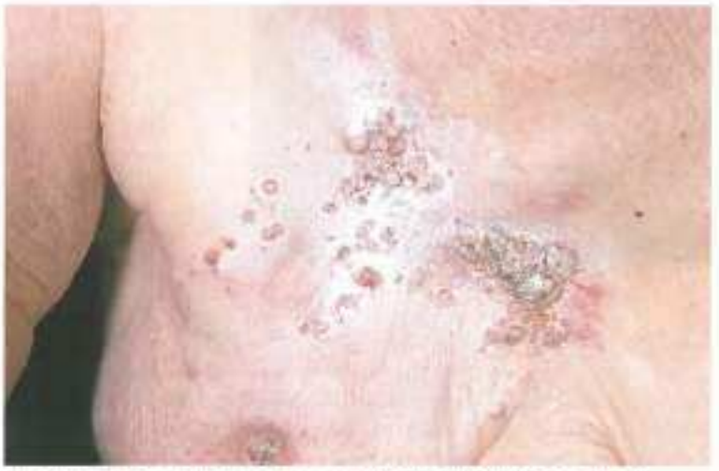


Fig. 22.161 Metastatic breast cancer. Multiple papules and nodules are present from a carcinoma of the breast.

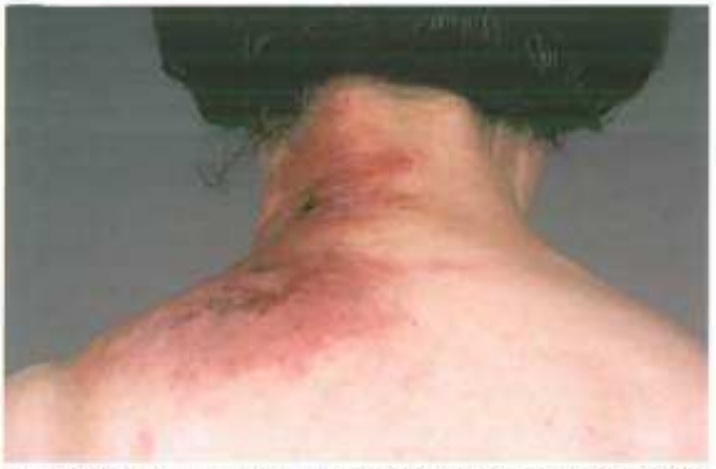


Fig. 22.162 Carcinoma en cuirasse. Localized spread from a carcinoma of the breast has resulted in a red, indurated mass around the neck and upper back.

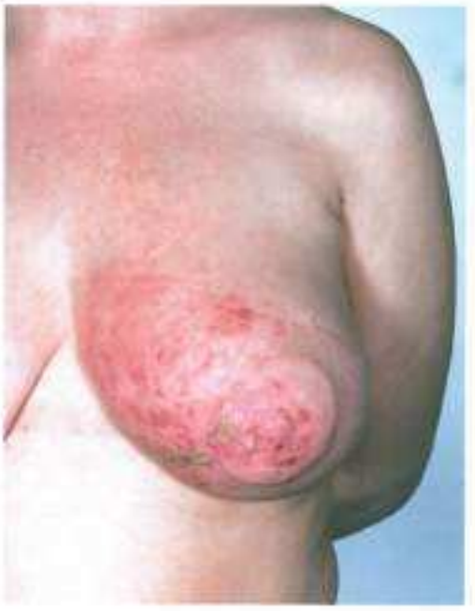


Fig. 22.163 Metastatic adenocarcinoma of the breast. The whole area around the breast is infiltrated with red papules forming a diffuse plaque, which is sometimes known as carcinoma erysipeloides or en cuirasse.

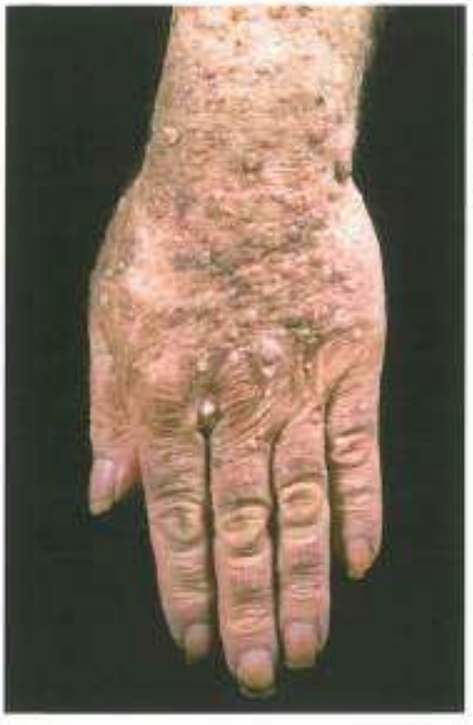


Fig. 22.164 The sign of Leser–Trélat. The sudden onset of a large number of pruritic seborrhoeic warts may be associated with malignancy, in this case carcinoma of the stomach.

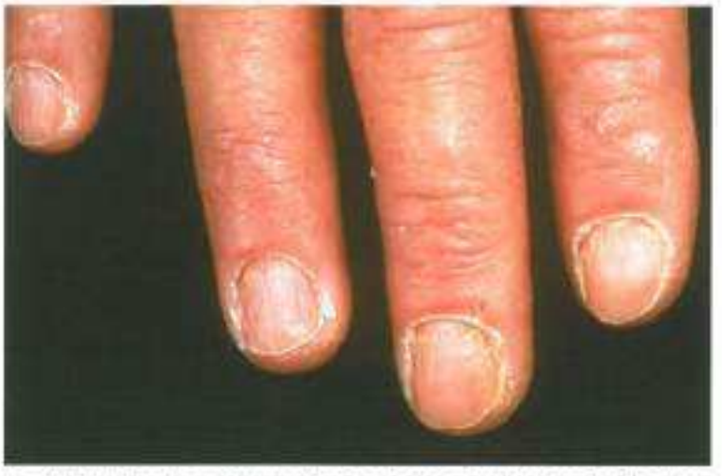


Fig. 22.165 Bazex's syndrome. This is a violaceous erythema and scaling of the peripheries with paronychia associated with a squamous cell carcinoma. (Courtesy of Drs Sarah Vaughan Jones and David McGibbon.)

tumour (carcinoma en cuirasse (Figs 22.162 and 22.163) with breast carcinoma) and Paget's and extra-mammary Paget's disease. Secondary deposits are most commonly from the lung, colon, breast, ovary, kidney and stomach. They usually occur on the anterior trunk or scalp. Sister Mary Joseph's nodule is a deposit in the umbilicus associated with carcinoma of the stomach. Non-Hodgkin's lymphoma and the leukaemias (especially myelomonocytic) may also involve the skin.

4. **Paraneoplastic dermatoses** Most of these are described elsewhere, but a convenient list is:
   - **Papulosquamous disorders**
     - Acanthosis nigricans
     - Tripe palms
     - Leser–Trélat. This is the sudden development of a large number of seborrhoeic warts (Fig. 22.164) associated with generalized pruritus.
     - Bazex's syndrome. *Bazex's syndrome (paraneoplastic acrokeratosis)* is the association of a squamous cell carcinoma of the upper respiratory tract or gastrointestinal tract with cervical lymphadenopathy with a violaceous erythema and scaling of the peripheries, especially the ears, nose, hands (Fig. 22.165) and feet. It becomes hyperkeratotic and there is a keratoderma of the palms and soles and a paronychia with nail dystrophy. It may become generalized and include the face and have rather an eczematous or lupus erythematosus-like appearance.
     - Acquired ichthyosis

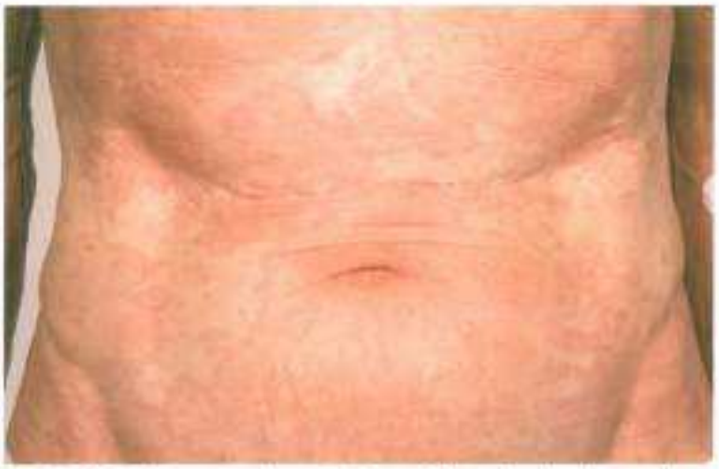


Fig. 22.166 Erythema annulare centrifugum. This man had a widespread figurate erythema; on investigation, he was found to have a carcinoma of the rectum.

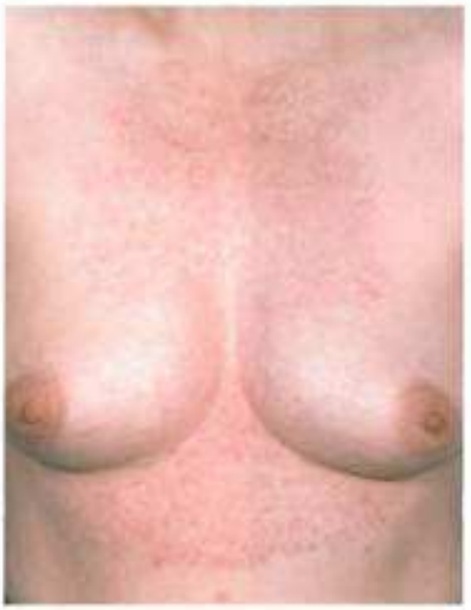


Fig. 22.167 Reticular erythematous mucinosis. A reticular erythema with a mucinous and round cell dermal infiltrate occurs on the front of the chest in females, sometimes with a monoclonal paraprotein. It responds to antimalarial drugs.

- **Autoimmune phenomenon**
  - Dermatomyositis
  - Antiepiligrin mucous membrane pemphigoid
  - Paraneoplastic pemphigus
  - Epidermolysis bullosa acquisita
- **Neutrophilic dermatoses**
  - Sweet's syndrome
  - Pyoderma gangrenosum
- **Reactive erythemas**
  - Erythema gyratum repens
  - Necrolytic migratory erythema
  - Erythema annulare centrifugum (Fig. 22.166)
- **Dermal proliferative disorders**
  - Multicentric reticulohistiocytosis
  - Necrobiotic xanthogranuloma
- **Deposition disorders** (see below)
  - Scleromyxoedema
  - Amyloid
- **Hair**
  - Acquired hypertrichosis
  - Lanuginosa acquisita
- **Generalized pruritus**

Malignant monoclonal gammopathies including multiple myeloma and Waldenström's macroglobulinaemia may be associated with a proliferation of the malignant plasma cells in the skin but may also produce a protein related to the primary M protein, such as amyloid or cryoglobulins. Paraneoplastic phenomena which are described elsewhere include scleromyxoedema, scleredema of Buschke, necrobiotic xanthogranuloma, plane xanthomas, Schnitzler's syndrome, necrobiotic xanthogranulomas, POEMS and *follicular cutaneous spicules* due to deposits of paraproteins on the nose and sometimes on the scalp, neck and extremities. Other less strongly associated conditions include pyoderma gangrenosum, Sweet's disease, leukocytoclastic vasculitis, neutrophilic dermatosis, erythema elevatum diutinum, subcorneal pustular dermatosis, paraneoplastic mixed bullous disease, epidermolysis bullosa acquisita, xanthoma disseminatum and REM (*reticular erythematous mucinosis*) syndrome (Fig. 22.167). The latter is characterized by asymptomatic erythematous reticulated macules or indurated papules on the front or back of the chest, which may be exacerbated by sun exposure (when it may cause burning). It may also be related to autoimmune diseases (particularly lupus erythematosus, because IgM is found at the dermo-epidermal junction), HIV and breast and colon cancer.

MALIGNANT ACANTHOSIS NIGRICANS

A paraneoplastic disorder of hyperkeratosis, pigmentation, skin tags and velvety thickening of the skin.

Aetiology

The skin changes may result from an oversecretion of a pituitary peptide. When associated with malignant disease, it is usually caused by an adenocarcinoma but occasionally a lymphoma. The histopathology is very similar to that of a flat seborrhoeic wart.

Clinical Features

Symptoms

There is a thickening of the skin in the flexures.

Morphology

The skin is pigmented, thickened and feels rather velvety. Skin tags and warty excrescences are present.

Distribution

It occurs symmetrically in the flexures (Fig. 22.168), notably the axillae, umbilicus, groins and anogenital area. The changes are more severe and

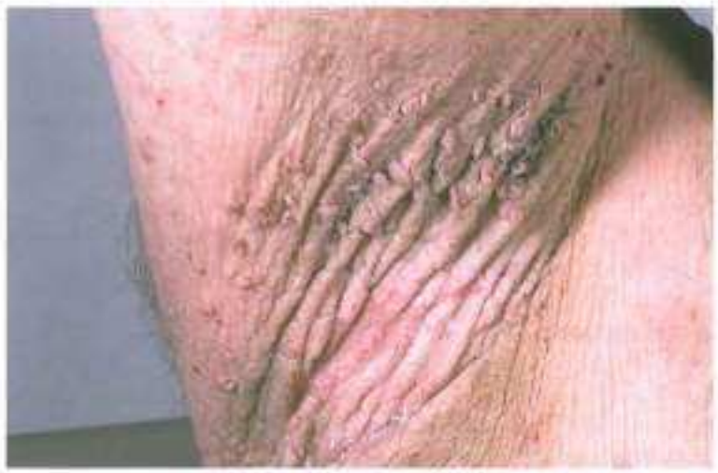


Fig. 22.168 Malignant acanthosis nigricans. Skin tags and warty excrescences occur in the flexures, with hyperpigmentation and thickening of the skin.

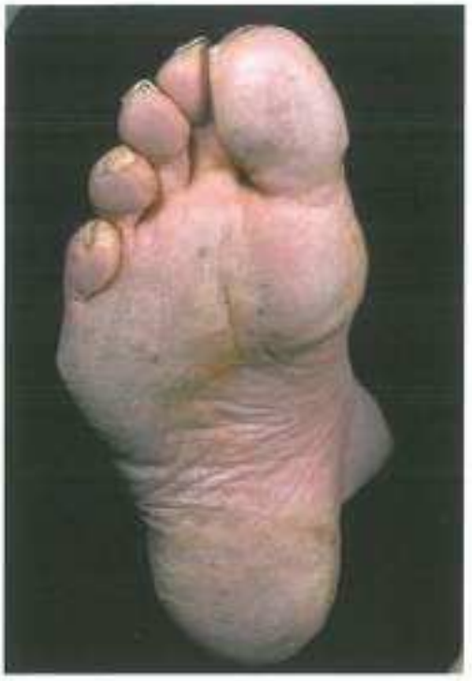


Fig. 22.169 Malignant acanthosis nigricans. The plantar skin is hyperkeratotic and thickened. This man had a carcinoma of the stomach.

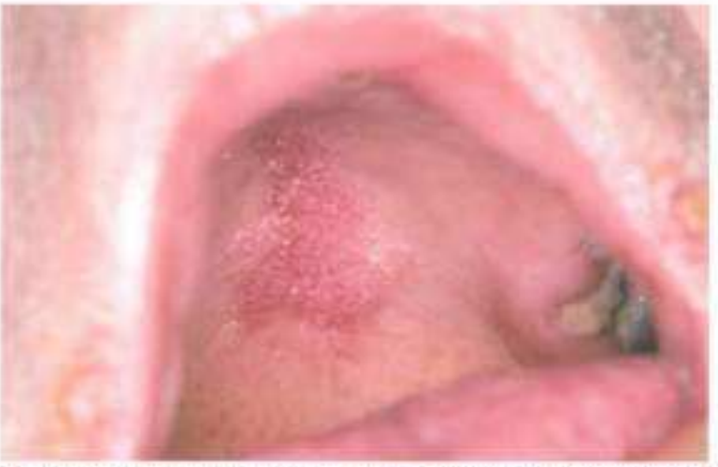


Fig. 22.170 Malignant acanthosis nigricans. The mucous membranes may be involved. There is a warty plaque on the palate.

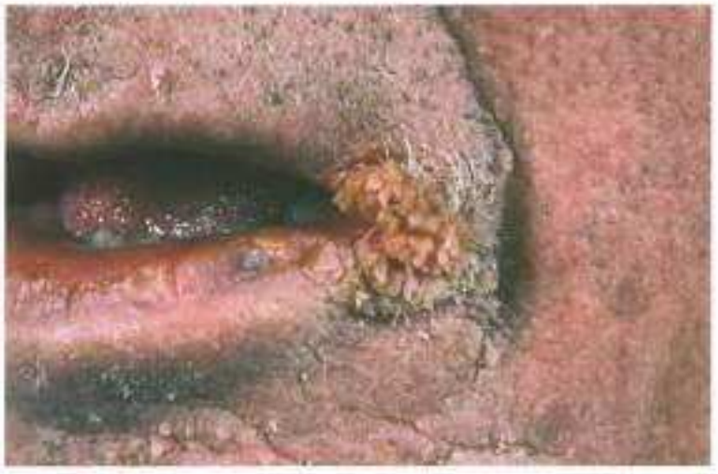


Fig. 22.171 Malignant acanthosis nigricans. Mucous membrane involvement is common. There are warty lesions at the corners of the mouth.

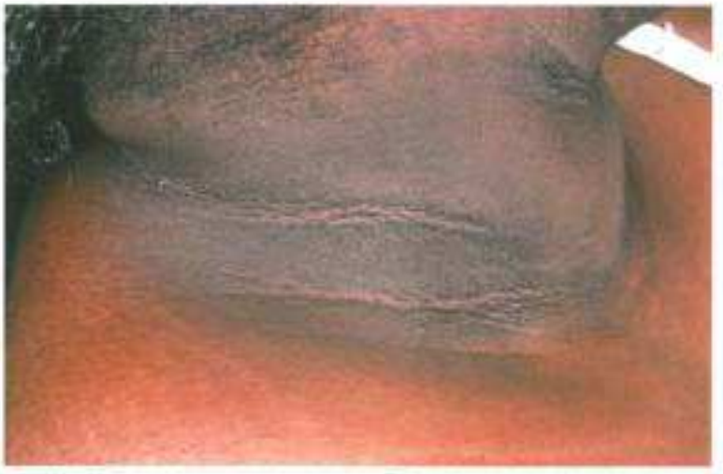


Fig. 22.172 Pseudoacanthosis nigricans. There is a velvety thickening and hyperpigmentation of the flexures associated with obesity and insulin resistance. It is quite harmless.

extensive (even universal) in malignant as opposed to pseudoacanthosis nigricans. The backs of the hands can be involved and the palmar and plantar (Fig. 22.169) skin may be grossly thickened. There may be generalized pruritus. The hair may be shed and the nails may be brittle or ridged. The mucous membranes (Fig. 22.170) and mucocutaneous junctions are involved in half of the cases, and warty thickening around the mouth (Fig. 22.171) and eyes is characteristic. The eruption may precede the symptoms of the underlying carcinoma by several years.

Management

It is important to distinguish the benign form (pseudoacanthosis nigricans) from the malignant. The onset is much earlier in the former and is associated with obesity and insulin resistance (Fig. 22.172). If malignant disease is suspected, extensive investigations must be undertaken to determine the cause. Resection of the tumour may be associated with resolution of the cutaneous findings, although recurrence is high.

NECROLYTIC MIGRATORY ERYTHEMA

A rare disorder of stomatitis, weight loss, anaemia, diabetes mellitus and a figurate erythema associated with a glucagon-secreting tumour of the alpha pancreatic islet cells, but also with alcoholic cirrhosis and haemochromatosis.

Aetiology

The mechanism by which the glucagonoma causes the skin eruption is not known, but possibly sustained gluconeogenesis from the high glucagon levels leads to amino acid deficiency, epidermal protein deficiency and necrolysis. Some patients have improved with intravenous amino acids and correction of essential fatty acid and zinc deficiency. The disorder is most common in middle-aged women. There are very high glucagon levels and these are usually secondary to a glucagon-secreting islet cell tumour of the pancreas, but aberrant glucagon-secreting tumours have been described. Necrolytic migratory erythema may occur without

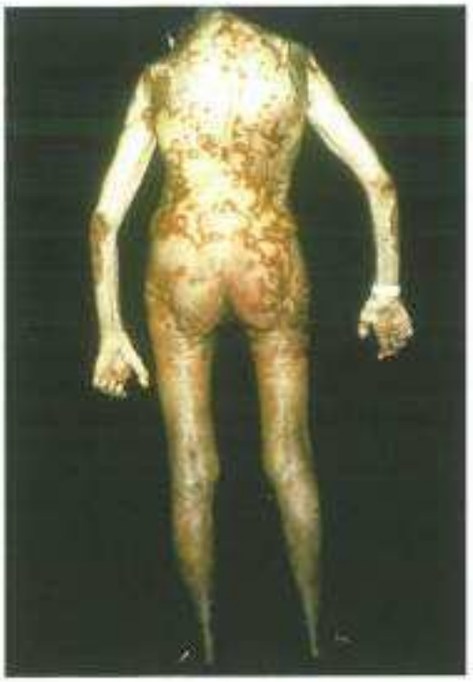


Fig. 22.173 Necrolytic migratory erythema. An annular migratory erythema occurs, which blisters and becomes eroded. (Courtesy of Dr C. Mallinson.)

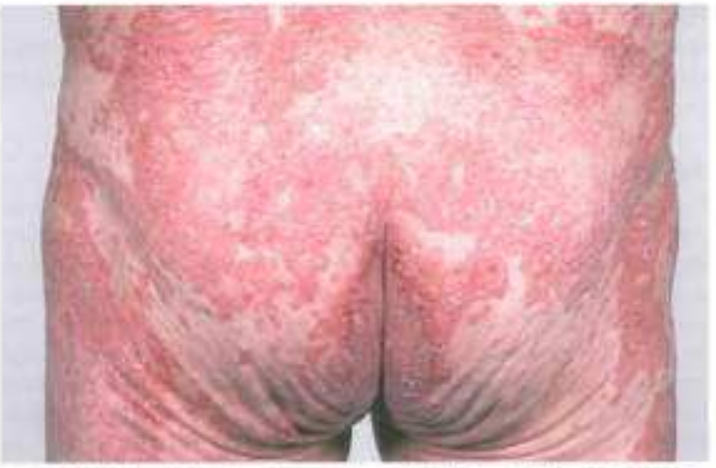


Fig. 22.174 Necrolytic migratory erythema. A striking, red, figurate erythema is present, with erosions perianally. The lesions were migratory. (Courtesy of Dr Michèle Clement.)

glucagonoma, particularly with malnutrition (pseudoglucagonoma syndrome). Thus high glucagon levels also occur with liver disease without glucagonoma, where the hepatocellular dysfunction leads to reduced degradation of glucagon and an increase in arachidonic acid and its metabolites in the epidermis. Possibly, trauma causes the release of these substances and, therefore, the rather inflammatory nature of the lesions. In addition these patients have hypoalbuminaemia and possibly this potentiates the release of arachidonic acid by glucagon; since albumin is the main carrier for zinc and essential fatty acids, this may also cause their deficiency. There are clinical similarities between necrolytic migratory erythema, acrodermatitis enteropathica and the protein energy malnutrition seen in complicated cystic fibrosis. Histology of the skin lesions shows necrolysis of the outermost cell layers and cleft formation. Dyskeratosis and acanthosis are present in older lesions. There is a lymphocytic infiltrate, particularly around blood vessels in the dermis.

Clinical Features

Symptoms

There is weight loss, diarrhoea, a sore mouth and tongue and a burning migratory skin rash.

Morphology

There are annular or circinate lesions (Figs 22.173 and 22.174) that start as an erythema which blisters and erodes, leaving postinflammatory hyperpigmentation. The lesions are migratory. Each takes a couple of weeks to evolve and heal.

Distribution of necrolytic migratory erythema

The lesions gradually extend from the lower abdomen, groin, perineum, buttocks and thighs. The tongue is raw and smooth (Fig. 22.175) and there is circumoral crusting.

Systemic signs

Venous thromboses, anaemia, wasting, fatigue and psychiatric disturbances are common. Most patients have diabetes without ketoacidosis or abnormal glucose tolerance.

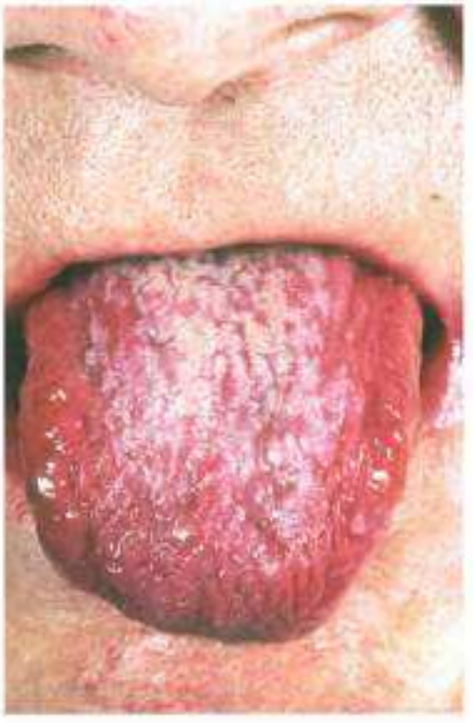


Fig. 22.175 Necrolytic migratory erythema. The tongue is sore, red, raw and smooth surfaced. There is also weight loss, diabetes mellitus and a figurate erythema associated with a glucagon-secreting pancreatic tumour. (Courtesy of Dr Ian McCallum.)

Management

Skin biopsy from the edge of an early lesion may show hydropic degeneration of swollen epidermal cells, necrosis of the superficial epidermis, and a split between the stratum corneum and epidermis, viz. a similar picture to zinc, fatty acid deficiency and pellagra. There is glycosuria, hyperglycaemia, raised glucagon levels, panhypoaminoaciduria and normochromic normocytic anaemia. Pancreatic and hepatic scans and arteriography should help locate the tumour. If the glucagonoma has not metastasized, surgery may be curative. Somatostatin or its analogues may temporarily inhibit glucagon secretion.

PAGET'S DISEASE

A malignant disorder of the nipple and areola always associated with a carcinoma of the breast or, more rarely, an extramammary cutaneous change sometimes associated with malignancy.

Aetiology

Paget's disease of the nipple and areola is invariably associated with an underlying invasive or intraduct carcinoma of the breast. Extramammary Paget's disease is much less common but is found around the anus or genitalia or both. It is usually, but not invariably, associated with carcinoma of the cutaneous adnexae or of the bowel/genitourinary tract. The former may represent an in situ malignant change in the intraepidermal component of the sweat duct and the latter an epidermotrophic metastasis from a distant neoplasm such as a carcinoma of the bowel, endocervix, bladder or prostate. Extramammary Paget's disease may also occur in the axillae, oral cavity, external auditory meatus (from a ceruminous gland carcinoma), umbilicus and eyelid (associated with a carcinoma of Moll's gland).

Clinical Features

Symptoms

The lesion may be sore and weep.

Morphology

Well defined, slightly raised and red with some scaling and fissuring.

Distribution

Only one breast is affected. Initially the nipple is involved first (Fig. 22.176) and then the areola (Figs 22.177 and 22.178).

In extramammary Paget's disease, it occurs around the anus (Fig. 22.179), vulva (Fig. 22.180), scrotum and groin (Fig. 22.181) and gradually extends.

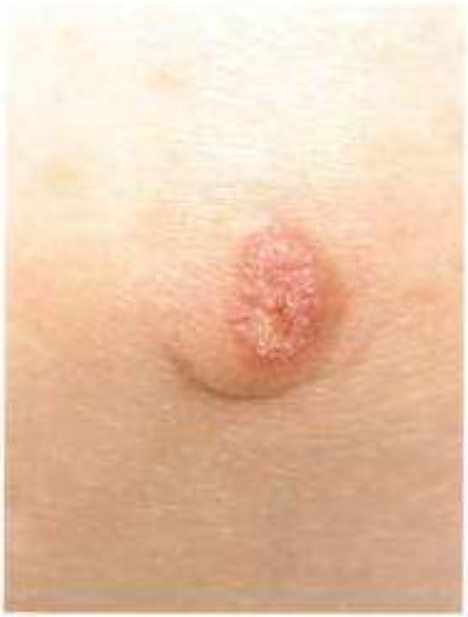


Fig. 22.176 Paget's disease of the nipple. There is a very well-defined, slightly raised, red, scaly plaque on the areola. (Courtesy of Dr A. C. Pembroke.)

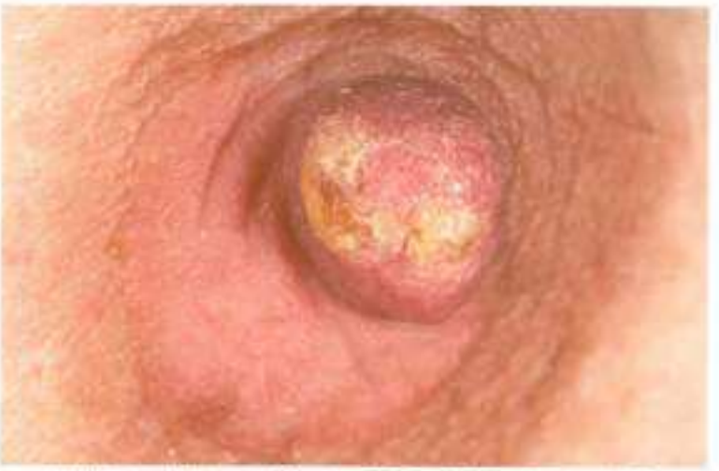


Fig. 22.177 Paget's disease of the nipple. The nipple is red and scaly. The areola is partly thickened. The margin is very well defined. A biopsy is mandatory.

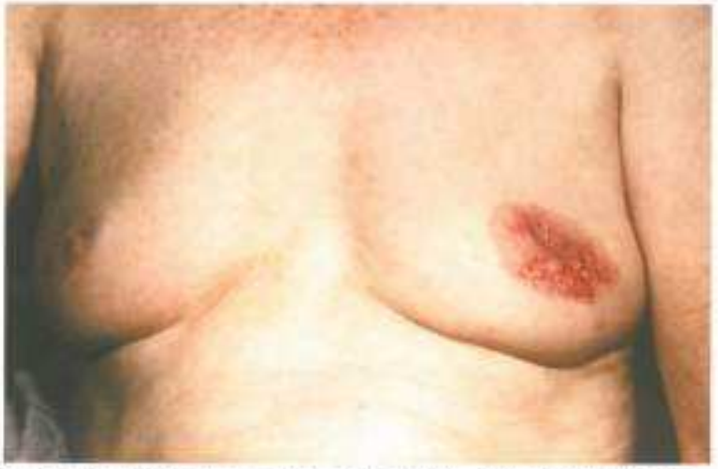


Fig. 22.178 Paget's disease of the nipple. The presentation here is late. The whole of the nipple and the areola is involved. It is unilateral.

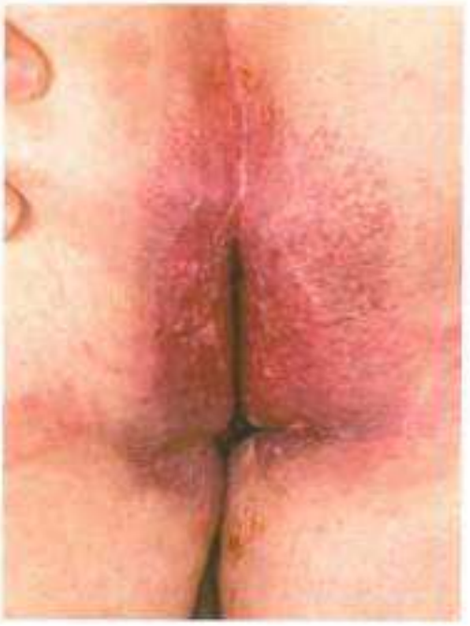


Fig. 22.179 Extramammary Paget's disease. The eruption is usually mistaken for eczema. However, the skin is raw and eroded, unlike eczema. The patient may have underlying malignant disease. Rectal adenocarcinoma is the most common, but the bladder or prostate may be the source. (Courtesy of Dr A. C. Pembroke.)

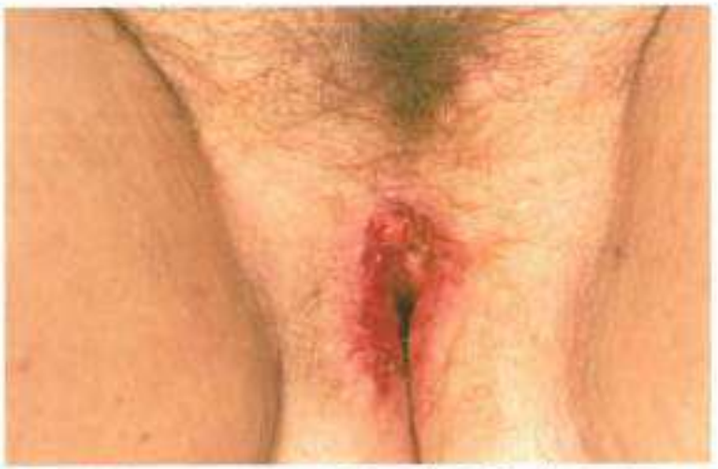


Fig. 22.180 Extramammary Paget's disease. A well-defined, red, scaly plaque is present around the vulva.

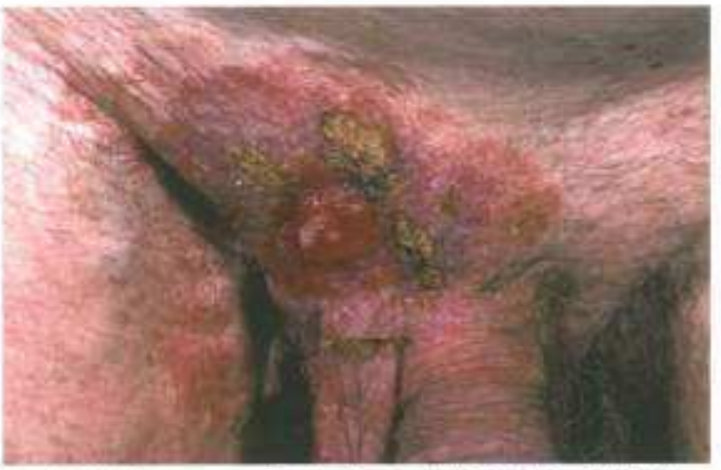


Fig. 22.181 Extramammary Paget's disease. In this case, the well-defined plaque of Paget's disease surrounds the tumour of an adnexal carcinoma.

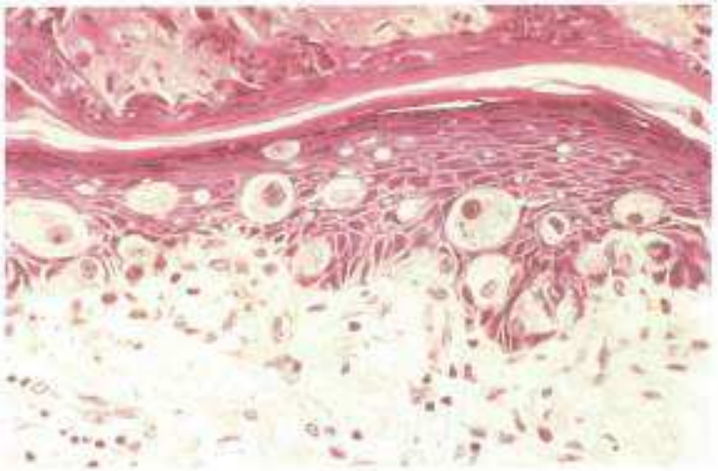


Fig. 22.182 Paget's disease of the nipple. There is superficial crusting. The irregular epidermis is infiltrated by cells with abundant, pale-staining, granular cytoplasm and large, oval, vesicular nuclei with prominent nucleoli.

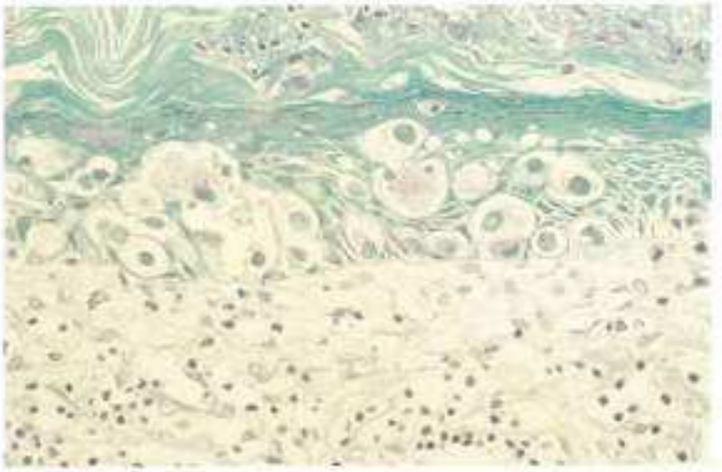


Fig. 22.183 Paget's disease of the nipple. The cytoplasm of the tumour cells contains magenta-coloured, diastase-resistant, periodic acid–Schiff-positive granules.

Management

A biopsy is mandatory. The epidermis in both mammary and extramammary Paget's disease is infiltrated by variable numbers of large cells with abundant pale staining cytoplasm and prominent oval vesicular nuclei with conspicuous eosinophilic nucleoli (Fig. 22.182). These cells may be present singly, in clusters or may replace the epithelium totally. They show a diastase-resistant, PAS-positive reaction (Fig. 22.183). The cytoplasm may also show a variably positive Alcian blue staining reaction, which distinguishes Paget's disease from an atypical Bowen's disease or in-situ superficial spreading malignant melanoma. In some instances, the dermis may be infiltrated by malignant cells from the underlying neoplasm.

It is essential to search for the underlying malignant disease and to treat it. This may not be found with extramammary Paget's disease and treatment of the cutaneous eruption may be difficult. Plastic surgery is the treatment of choice, but frequently the lesion has spread extensively and Moh's chemosurgery should be considered. Radiotherapy and topical 5-fluorouracil are essentially ineffective. CO_2 laser therapy of extramammary Paget's disease guided by photodynamic use of aminolaevulinic acid ointment applied to the skin and illuminated by a Wood's light has been described. Imiquimod is reported as being of benefit.

Generalized pruritus

Itching is a common symptom. The term *generalized pruritus* implies itching without evidence of a pruritic skin disease such as scabies, eczema, urticaria, lichen planus, pediculosis, dermatitis herpetiformis, drug eruptions or bullous pemphigoid. On examination, there are either no abnormal physical signs or only excoriations as a result of scratching. A careful history and examination with appropriate investigations must be undertaken. The more common causes of generalized pruritus are:

- **Uraemic pruritus** Pruritis occurs in most patients on dialysis. There is sometimes secondary hyperparathyroidism and the itch has been reported as disappearing after parathyroidectomy. The itch may be related to substance P, a neurotransmitter in afferent sensory neurones. Capsaic acid depletes substance P and is sometimes helpful.
- **Cholestasis** The pruritus in cholestasis is associated with high plasma levels of bile salts but there is no correlation between concentration and severity of itch. Causes are primary biliary cirrhosis, extrahepatic obstruction, cholestasis of pregnancy and cholestatic drugs. Drugs that lower bile salts, such as cholestyramine, may improve the pruritus.
- **Thyroid disorders** The pruritus of thyrotoxicosis may be caused by increased cutaneous blood flow, thereby raising the skin temperature

and possibly reducing the threshold of the skin to itch. The pruritus of hypothyroidism may be largely caused by the dry skin.

- **Diabetes mellitus** Generalized pruritus associated with diabetes has been reported but is not common.
- **Haematological** Iron deficiency anaemia, lymphoma and myeloproliferative disease are frequent causes. With polycythaemia rubra vera there may also be aquagenic urticaria (which may precede objective evidence of the disease by some years – although the JAK2 genetic mutation may be worth searching for). The pruritus of polycythaemia is most distressing, but may be controlled by PUVA.
- **Drugs** Opiates and derivatives and aspirin may cause itching without cutaneous physical signs.
- **Senile pruritus** Sometimes no specific disorder is found, particularly in the elderly, and the skin is often dry, scaly and has lost its elasticity. It is postulated that the sensation of itching is a result of arteriosclerosis of the blood vessels that supply the nervous tissue in the skin. Although the degree of irritation may be intense, it is remarkable how often there are no signs of excoriation on the skin. Management is with local anaesthetics and cooling agents such as camphor, menthol and phenol. Antihistamines such as hydroxyzine hydrochloride and doxepin may be helpful. Reduction of bathing and the use of emollients should be encouraged.
- **Prurigo** and its variant nodular prurigo are described here.

PRURIGO

A chronic disorder of generalized itching and widespread excoriations.

Aetiology

The term prurigo is used when there is no cutaneous or systemic explanation for the itching. Emotional factors are suspected, although not proven. It occurs in both sexes, but more especially middle-aged women. Confusingly, atopic eczema is known as Besnier's prurigo when excoriations predominate, and the itch of pregnancy, which starts at the end of the second trimester and persists until just after delivery, is known as prurigo of pregnancy. However, these are unrelated. The pathology of prurigo reveals non-specific inflammation initially but in nodular prurigo, there is gross thickening of the epidermis and hyperkeratosis is notable with a moderately dense mixed inflammatory infiltrate in the dermis.

Clinical Features

Symptoms

Itching.

Morphology

There are small excoriated papules (Fig. 22.184) which in chronic disease may lead to nodule formation (Fig. 22.185).

Distribution

The extensor aspects of the limbs, upper trunk (Fig. 22.186) and buttocks.

Management

Superpotent topical steroids with occlusive bandaging of the limbs may be useful. Nodular prurigo may be treated with intralesional steroids. Sedative antihistamines, especially hydroxyzine hydrochloride, are helpful. Ultraviolet light and PUVA are sometimes helpful. Psychological remedies have a variable success. Thalidomide and subsequently (because it has less side effects) lenalidomide may prove to be effective.

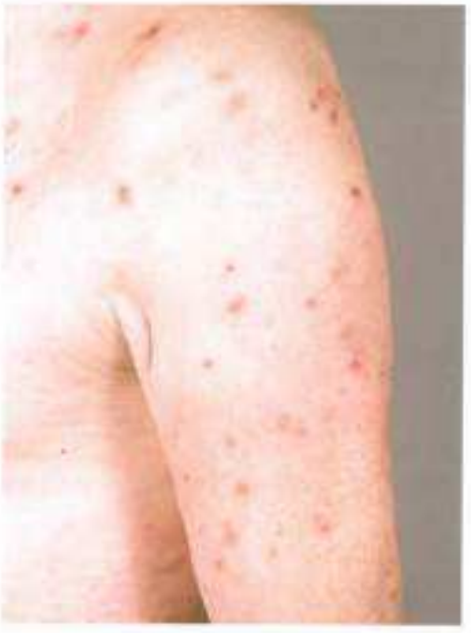


Fig. 22.184 Prurigo. There are many excoriations of the skin. It is necessary to search for a systemic cause for the pruritus. If negative, the condition is called prurigo.

Fig. 22.185 Nodular prurigo. The limbs and upper back are covered with nodules. Treatment is unsatisfactory but ultraviolet light may be helpful.

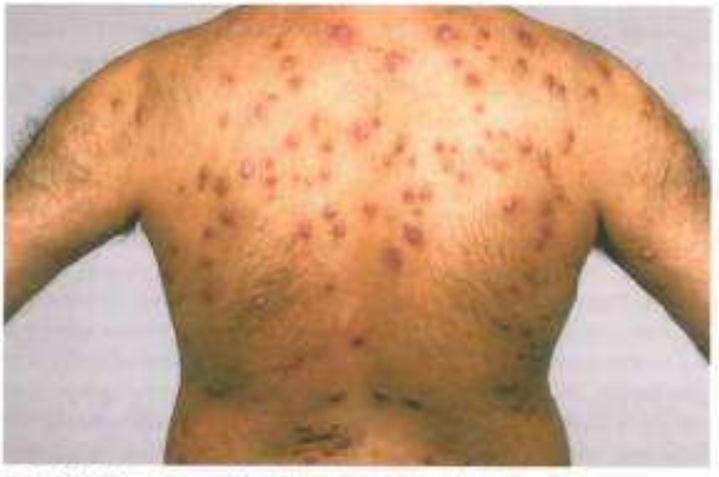


Fig. 22.186 Nodular prurigo. Chronic scratching of the skin will lead eventually to nodule formation. The lesions have a warty excoriated surface.

Skin manifestations of disordered circulation

23

Gravitational/Stasis eczema and ulceration

A common disorder of the lower limbs that arises from venous hypertension and results in a gravitational syndrome of increased perfusion of the tissues, which produces various abnormalities including eczema, oedema, inflammation, induration, ulceration and sometimes fibrosis and calcification of the skin.

Aetiology

Following contraction of the gastrocnemius and soleus muscles during exercise, blood is returned from the leg to the heart by three sets of veins: deep, superficial and intercommunicating (perforating). Valves prevent the blood from returning downwards. If this system fails in any of its components, venous hypertension results, which causes distension and elongation of the capillary loops. Fibrinogen leaks into the tissues through the widened endothelial pores and fibrin is laid down in the capillaries to form a 'cuff', which limits the diffusion of oxygen and other nutrients to the skin. In addition, white cells accumulate during periods of immobility, plug the capillaries and thus contribute to local ischaemia.

The most common causes of failure of the system are:

- **Venous thrombosis** This may occur during any period of immobility, especially following surgery, during labour or recuperation after a fracture (especially of the hip). The contraceptive pill also predisposes to thrombosis. The thrombus blocks the proximal flow of blood in the deep system, creating a diversion through the perforators into the superficial veins, which dilate so that the valves are no longer competent (i.e. cannot close completely). The deep venous thrombosis may or may not have been clinically apparent at the time. As techniques for the prevention of deep venous thrombosis during medical procedures improve, this disorder is becoming less common.
- **Absent valves** This is dominantly inherited and presents in younger patients. The valves are absent rather than damaged.
- **Muscle disease** A compromised muscle pump may result from neuromuscular disease, such as poliomyelitis, or from disuse atrophy of the muscles, as in severe arthritis.
- **Factor V Leiden mutation** The activated form of coagulation factor V is inhibited by activated protein C (APC) and this prevents excessive thrombus formation. This efficient negative feedback mechanism is disturbed in the factor V Leiden mutation (5% of the population), which alters one of the major APC cleavage sites and leads to APC resistance. The risk for deep vein thrombosis is increased fivefold.

Venous hypertension is common and more frequent in overweight females from lower socioeconomic groups. It occurs on the gaiter area of the lower leg, particularly around the ankle.

Clinical Features

There are a number of physical signs.

- **Eczema** These itchy, red, scaly patches (Fig. 23.1) respond well to potent topical glucocorticosteroids and to measures designed to reduce venous hypertension. However, a common complication is *dermatitis medicamentosa* (contact sensitization to topical medicaments) particularly from lanolin, parabens (a preservative), antibiotics, anaesthetics or rubber in elastic stockings. Neomycin, soframycin, framycetin and gentamycin are common antibiotic sensitizers and should not be prescribed for varicose eczema or ulceration. Topical tetracycline is usually safe. The diagnosis should be suspected if the varicose eczema or ulcer fails to improve or even deteriorates during treatment. The eczema becomes acute (Fig. 23.2) and *autosensitization* may result (Figs 4.27 and 4.28). This means a reaction of the skin, particularly the face (especially around the eyes), neck and arms to a contact allergic reaction

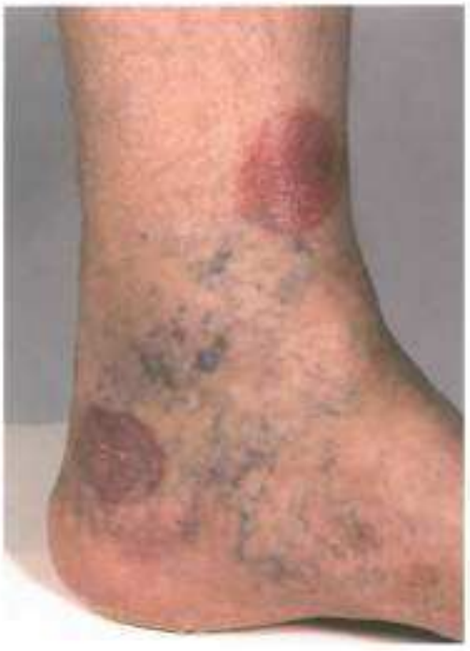


Fig. 23.1 Varicose eczema. Discoid patches of eczema are present in association with venous engorgement.

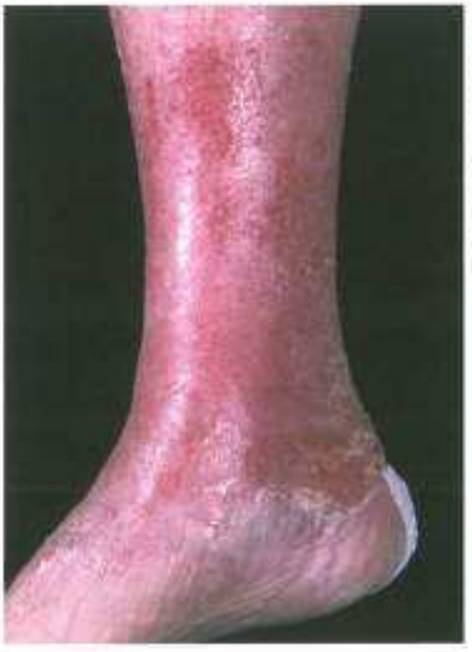


Fig. 23.2 Contact dermatitis. This man had become allergic to rubber in his elasticated compression stockings. There is a subacute weeping eczema in a diffuse distribution. The lower leg is a common site for contact sensitization.

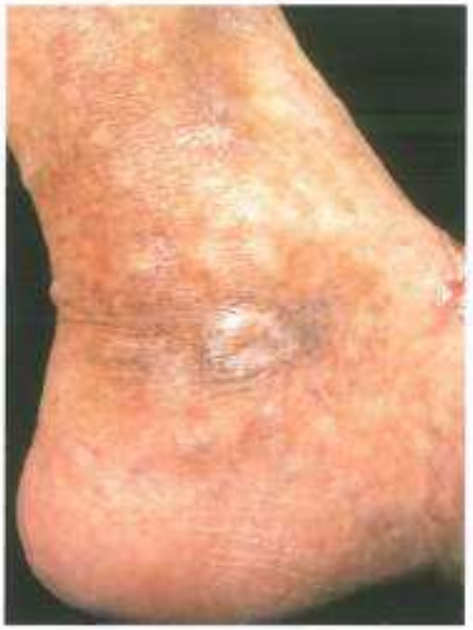


Fig. 23.3 Atrophie blanche. White plaques of sclerosis occur as a result of necrosis of the skin.

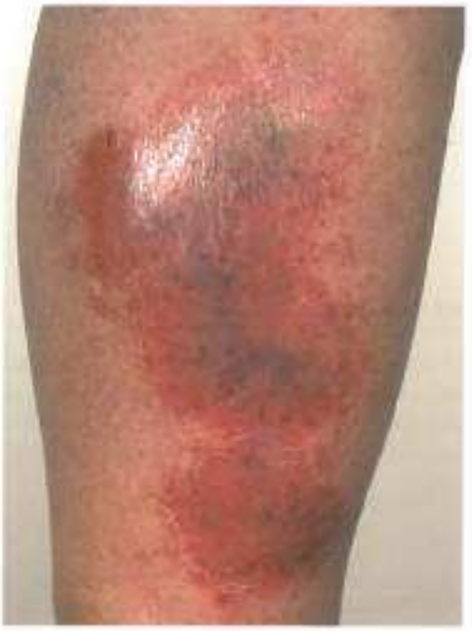


Fig. 23.4 Cellulitis. Erythema and oedema are present around the varicosities.

elsewhere on the body. This continues until the offending medicament is removed.

- **Atrophie blanche** This describes small, white plaques of sclerosis, often with a characteristic red stippling of the surface (Fig. 23.3). It is the result of necrosis of the skin and may follow thrombosis in the iliac veins or inferior vena cava.
- **Oedema** This is a result of venous hypertension, which may be aggravated by the general medical condition of the patient, for example in cardiac failure. Cellulitis (Fig. 23.4) is an early complication of oedema, from which fibrosis may result. Prolonged and neglected oedema leads ultimately to a condition known as *lipodermatosclerosis*, in which the skin feels indurated, woody and sclerodermatous. Eventually the leg looks like an inverted champagne bottle, with the upper two-thirds of the leg swollen but the lower third tapered (Fig. 23.5). The fibrosis may lead to fixation of the ankle joint and limitation of the muscle pump, which makes the condition worse.
- **Pigmentation** Discrete brown macules (Fig. 23.6), which usually merge into one another to produce diffuse areas of staining, are caused by haemosiderin deposition in the tissues, following the extravasation of red cells (stasis purpura), and by melanin deposition following inflammatory changes. This differs from capillaritis (Ch. 18), where prominent russet coloured patches of pigmentation (due to haemosiderin) follows the extravasation of red cells (petechiae) secondary to pericapillary inflammatory changes (Fig. 23.7) but which nonetheless may be associated with venous insufficiency.
- **Venous flare** Tortuous dilated veins around the ankles are characteristic of venous hypertension (Fig. 23.8).
- **Varicosities** Varicose veins may or may not be present. Tortuous dilated 'blow-out' veins may result from previous venous thrombosis. They are common, increase with age and may cause discomfort with prolonged standing, warmth, premenstrually and with pregnancy. Superficial varicosities (thread veins) may be present (Fig. 23.9).

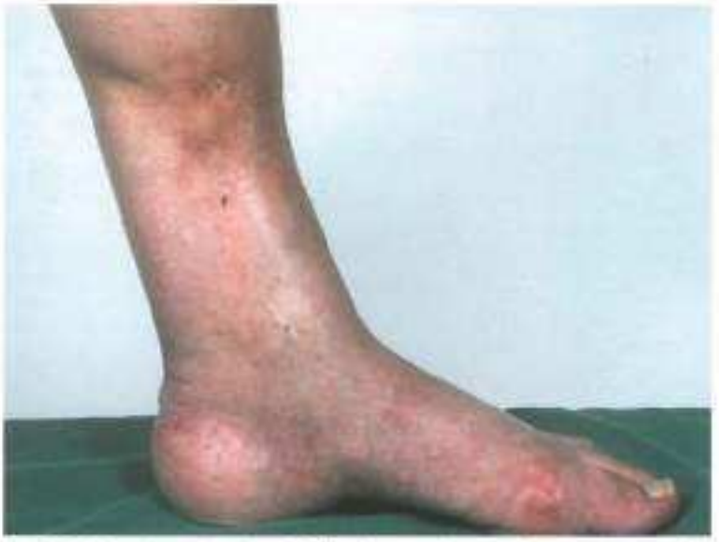


Fig. 23.5 Lipodermatosclerosis. Chronic venous hypertension, oedema and cellulitis may lead to fibrosis around the ankle, and woody induration, giving the appearance of an inverted champagne bottle.

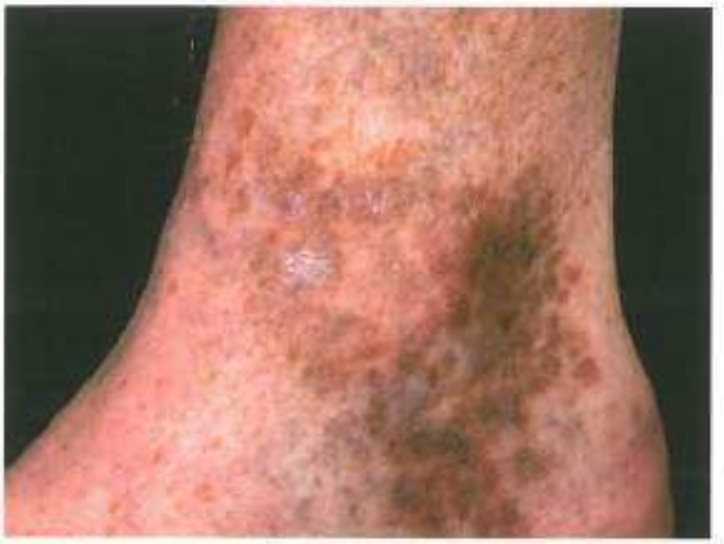


Fig. 23.6 Venous pigmentation. As a result of venous hypertension, red cells extravasate into the tissues and haemosiderin is deposited. Melanin is also present, secondary to inflammatory changes.

Fig. 23.7 Capillaritis. Although this may occur and be associated with venous insufficiency, on the legs, the clinical picture and pathology differ from that of venous hypertension.

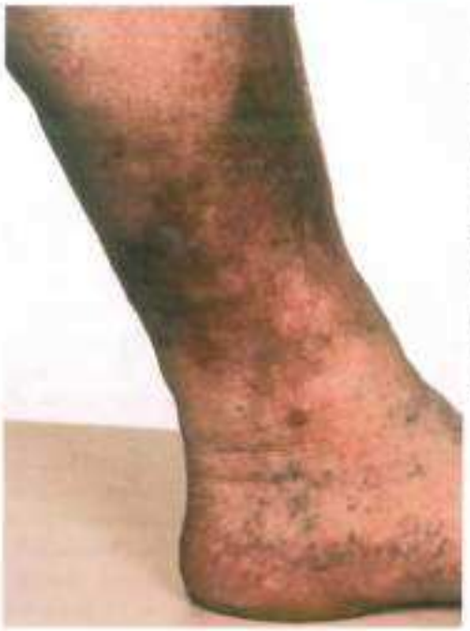


Fig. 23.8 Venous flare. There are blue tortuous dilated veins around the ankle with haemosiderin and melanin pigmentation. The venous system is responsible for the return of blood from the periphery to the heart aided by the calf muscles, which act as a pump. Retrograde flow is prevented by one-way bicuspid valves located throughout the venous system.

- **Ulceration** This is the final physical sign of cutaneous malnutrition and represents breakdown of the epithelium. Ulceration is often precipitated in a compromised patient by minor injury or infection. The ulcers vary in shape and size and may be very large indeed: the smaller ones are sometimes very painful; the larger ones often painless. The margin of the ulcer is well defined but not raised, and the absence of a rolled or heaped-up margin differentiates it from a basal cell or squamous cell carcinoma. The base of the ulcer varies: some have a yellow slough oozing serum or pus, whereas others are red and haemorrhagic. The latter indicates improved oxygenation of the blood and, therefore, improved nutrition of the skin, which makes healing more likely (Figs 23.10 and 23.11). Venous ulcers occur around the medial and lateral malleoli, whereas ulcers in other sites may be arteriosclerotic in origin. Often both conditions coexist.

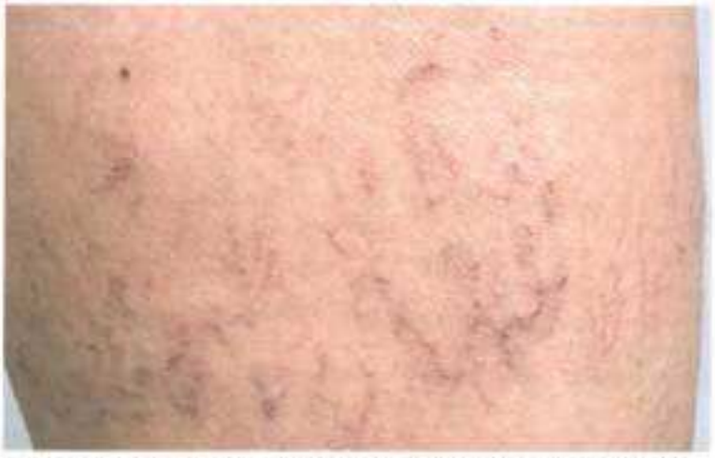


Fig. 23.9 Thread veins. Superficial (or sunburst) varicosities and telangiectasia are common in association with deeper varicosities. They may be treated with sclerosants such as sodium tetradecyl sulphate.

Fig. 23.10 Venous ulceration. This ulcer was in the classical site at the malleolus and has a well-vascularized base. Ulcers result from an interplay of tissue hypoxia, reduced transport of nutrients, formation of fibrin cuffs and trapping of growth factors secondary to venous hypertension.

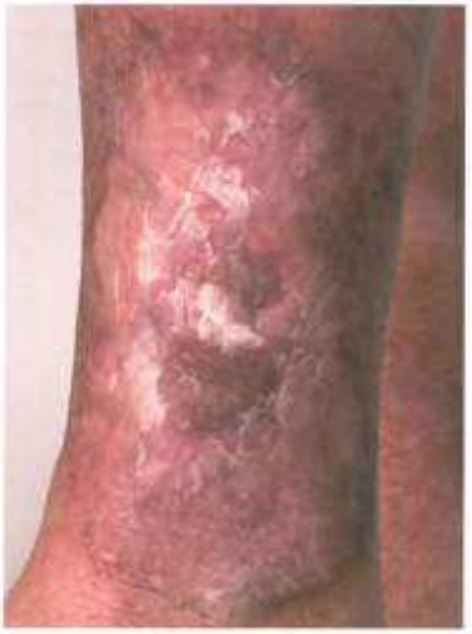


Fig. 23.11 Venous ulceration. The ulcer (Fig. 23.10) was healed after 3 months of compression therapy. Chronic venous insufficiency results from structural or functional abnormalities of the veins or their valves, venous obstruction or muscle pump failure.

- **Pseudo-Kaposi's sarcoma** This is an exaggerated stasis dermatitis that simulates Kaposi's sarcoma in being a well-defined purple plaque (Fig. 23.12). Histologically, there are an increased number of thick-walled vessels lined by plump endothelial cells, with extravasation of erythrocytes and deposition of haemosiderin.

Management

Venous ulceration is rewarding to treat (Figs 23.13 and 23.14) if the patient is motivated and there is continuity of medical care throughout the often prolonged course of the condition. The most essential therapy is the application of 30–40 mmHg pressure compression bandages to the lower limbs. Venous ulcers heal within 6 months in 50% and most heal within the year. Factors that are associated with failure to heal are large wound size, long duration of the ulcer, history of venous ligation or stripping, history of hip or knee replacement (probably acting as a marker of poor mobility and, therefore, calf pump dysfunction and the risk of deep vein thrombosis), an ankle brachial index of less than 0.8 and the presence of fibrin on most of the wound surface. Treatment involves:

- **Rest and elevation of the leg** Prolonged standing should be prohibited. The patient should be advised to rest the leg as much as possible, with the leg raised 12 inches (30 cm) above the hip to facilitate the venous return. Blocks to raise the end of the bed by 9–12 inches (20–30 cm) are very helpful.
- **Compression bandages** Bandages that deliver a pressure of 30–50 mmHg at the ankle are mandatory to prevent oedema and improve the effect of the muscle pump. The patient puts on the bandage first thing in the morning, before getting out of bed, and keeps it on until retiring at night. Compression therapy should be continued for 2 years after a deep vein thrombosis in order to reduce the rate of the post-thrombotic syndrome. Anticoagulants may reduce the rate of thromboses.
- **Exercise** Walking and heel-raising exercises, which bring about dorsiflexion and contraction of the calf muscles, are required for maintenance of the muscle pump.
- **Diet** Many of the patients are obese and reducing diets are of great benefit.
- **Full medical examination** Many patients in clinics for leg ulcer have general medical problems such as anaemia, malnutrition, hypertension and heart failure, which should be recognized and treated. Cessation of smoking, avoiding beta-blockers and skin grafting may be helpful.
- **Treatment of the eczema** Potent steroids (without antibiotics or local anaesthetics, which may sensitize the patients) are effective. Steroids, however, delay healing and should not be put on an ulcer.
- **Patch tests** These may detect sensitivities in patients with non-responsive varicose eczema and ulceration.
- **Treatment of infection** Cellulitis should be treated with appropriate systemic antibiotics. However, local infection of the ulcer itself does not respond well to systemic antibiotics; they should not be prescribed unless a beta-haemolytic streptococcal infection is present. In addition to causing sensitization, topical antibiotics are responsible for the occurrence of resistant strains of organisms. Measures for cleaning the ulcers, described below, should be adequate for dealing with most forms of infection.
- **Measurement** A diagram recording the length and breadth of the ulcer, and perhaps a polaroid photograph, help to assess progress.

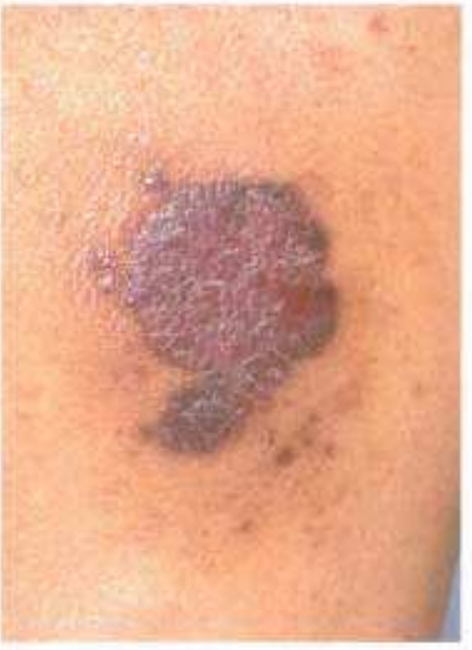


Fig. 23.12 Pseudo-Kaposi sarcoma. This is a pronounced stasis eczema. There is a well-defined purple plaque, which simulates clinical Kaposi's sarcoma.

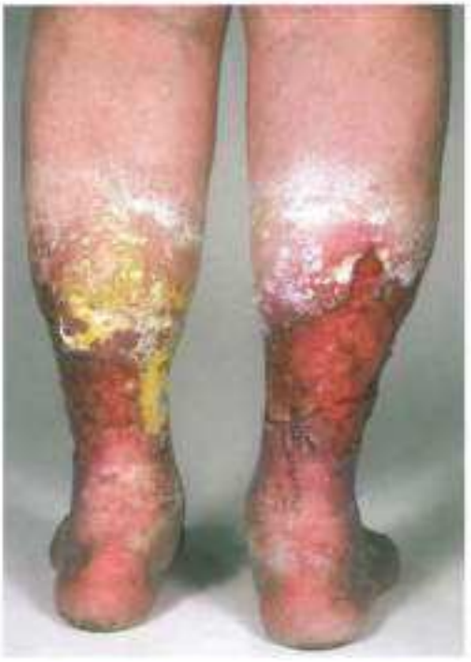


Fig. 23.13 Venous ulceration. These ulcers are large but still may be healed in outpatient departments with simple remedies such as gentian violet and potassium permanganate soaks.

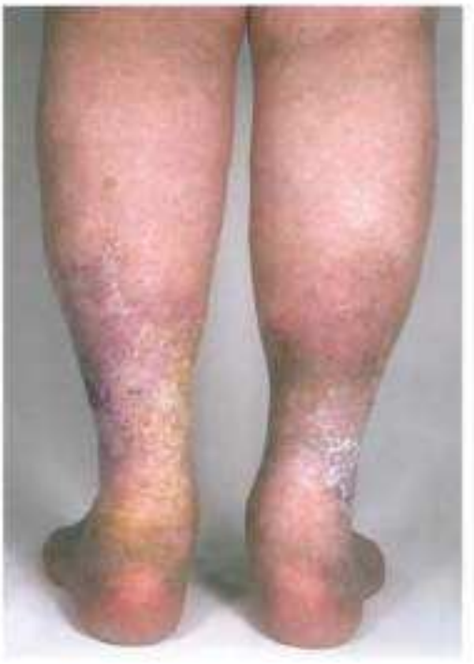


Fig. 23.14 Venous ulceration. It took 1 year to heal the ulcers (Fig. 23.13). Compression bandaging is an important component of therapy.

- **Duplex ultrasound** This permits direct visualization of the veins and the flow through the valves using echopulsing with Doppler velocity recording and is an essential investigation.
- **Local therapy** Granulation tissue results in wound contraction and re-epithelialization, which occurs from the periphery and from residual epithelial elements in the ulcer. It can be encouraged by (i) removal of the slough and necrotic debris, which otherwise impede healing. Mechanical debridement with forceps and scissors is generally more effective than topical preparations. (ii) The use of cleaning agents includes saline, chlorhexidine gluconate, povidone-iodine, potassium permanganate soaks, rosaniline dyes (0.5% aqueous gentian violet, carbofuschin and brilliant green), and oxidizing agents (hydrogen peroxide, benzoyl peroxide 20%).
- **Absorbent dressings** These are necessary for soaking up exudates and providing occlusion and thus a moist environment, which increases epithelialization (dry environments lead to scab formation and hinder healing). Paraffin gauze covered by a sterile gauze pad or non-adherent dressings are standard. Newer preparations are carbohydrate polymers as inert hydrophilic microbeads to absorb exudates, for example dextranomer powder or paste. Other polymers include cadexomer iodine, which releases iodine as it absorbs, and alginates, which become soluble in the presence of sodium ions. Geliperm, an inert polyacrylamide/agar hydrogel, has the advantage of being a transparent moist gel sheet through which the ulcer may be inspected.
- **Bandages** The use of bandages containing zinc oxide plus coal tar, or zinc paste in combination with calamine, clioquinol or ichthammol are helpful, especially if there is concomitant eczema. These are changed once or twice a week.
- **Treatment of the gravitational syndrome** Lipodermatosclerosis may be painful. It is sometimes relieved by stanozolol 5 mg twice daily (the blood pressure and liver function tests should be monitored), oxerutins 250 mg three times daily or intralesional triamcinolone. Open toe/below knee graded compression stockings are helpful.
- **Hospitalization** This may be necessary in some patients to enforce rest, to ensure elevation of the leg and to provide regular nursing care. It is especially helpful for large ulcers, some small painful ulcers and in the elderly, but it does take its toll in terms of time and expense.
- **Skin grafting** This is especially useful for large ulcers, either by the use of pinch grafts (the application of 0.5–1 cm pinches of skin taken under local anaesthesia from the thigh) or split skin grafts. Tissue engineered skin (living skin equivalent) is being explored as an alternative to split thickness skin grafting. It consists of type I bovine collagen and cultured allogeneic cells (keratinocytes and fibroblasts) isolated from human neonatal foreskin. It lacks the clinical rejection associated with an allogeneic cultured human skin equivalent.
- **Surgery** Consultation with a vascular surgeon is worthwhile, although the long-term effects of surgery are not spectacular. Surgery is available for perforating veins. Sclerotherapy is the injection of varicosities.

Arterial leg ulcers

Cutaneous malnutrition and ulceration of the skin caused by arterial insufficiency.

Aetiology

Ischaemia results from arteriosclerosis, a complex disorder with widespread implications, influenced by genetic, dietary and socioeconomic factors, as well as stress, smoking, diabetes mellitus and hypertension.

Clinical Features

Symptoms

Arterial leg ulcers are frequently painful, particularly when elevated and at night. The patient gets out of bed and walks about in order to obtain relief. Other symptoms of ischaemia are intermittent claudication, coldness, numbness, burning and paraesthesia secondary to an associated ischaemic neuropathy.

Signs

- **Skin** The skin is dry, scaly, thin and cool (Fig. 23.15). The colour is pale, cyanosed or blotchy. If the limb is elevated, the pallor is accentuated because of the poor performance against gravity.
- **Hair** The hair on the lower leg and toes is sparse or absent.
- **Nails** They are thickened, distorted and require less cutting.
- **Ulcers** Ulceration results from severe ischaemia. Ulcers are well defined, punched out (Fig. 23.16), deep and often have a thick necrotic slough. They occur primarily on the shin, heel, dorsum of the

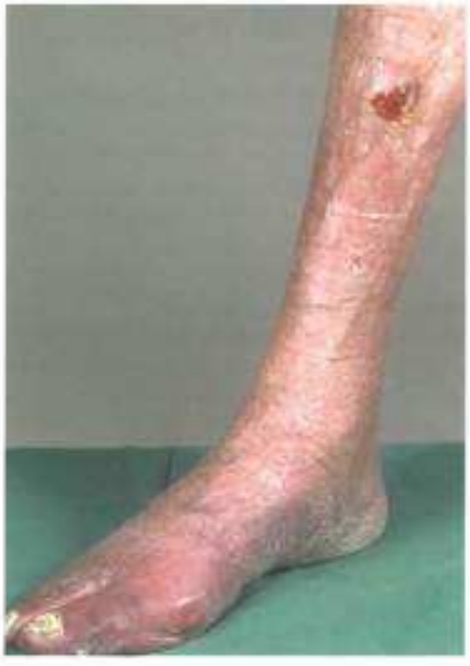


Fig. 23.15 Arterial insufficiency. The skin is dry, hairless and atrophic. The toes are cyanotic and the nails are dystrophic. The ulcer is on the shin; it is usually painful. The peripheral pulses were absent.

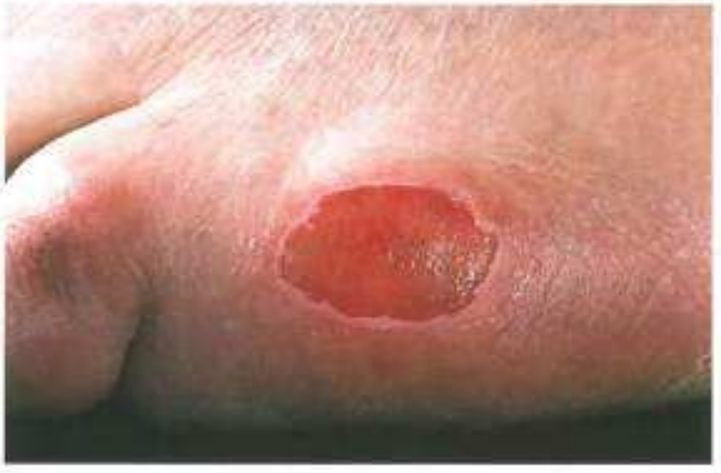


Fig. 23.16 Arterial insufficiency. This patient was diabetic. The ulceration is well defined and punched out in appearance. It was caused by ischaemia and also neuropathy. He was unaware that his shoes were too tight. (Courtesy of Prof. Mike Edmonds.)

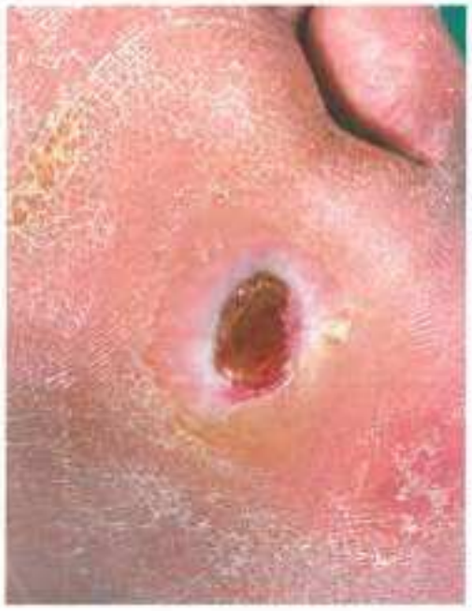


Fig. 23.17 Neuropathic ulceration. This patient was also diabetic. This is a classic site for a neuropathic ulcer. He had been on a long walk and his skin was insensible to the friction from his shoes. (Courtesy of Prof. Mike Edmonds.)

Fig. 23.18 Gangrene. The final stage of severe ischaemia is necrosis of the skin and subcutaneous tissue, as seen in the little toe.

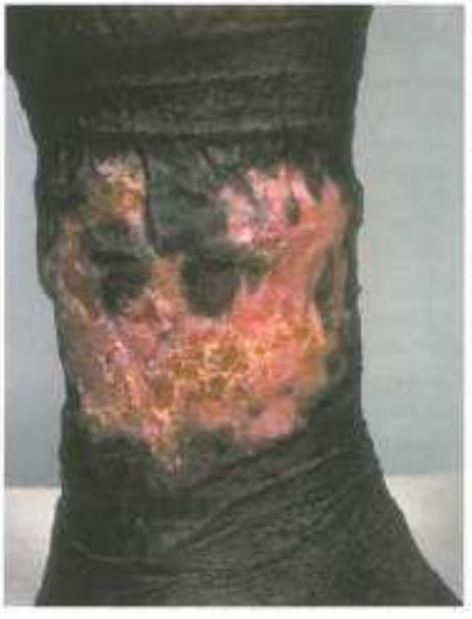


Fig. 23.19 Pyoderma gangrenosum. This condition is commonly misdiagnosed. It is a clinical diagnosis, because the pathology is not specific. The onset is sudden. The lesion is painful and the margin is heaped up and oedematous, but the characteristic blue margin is difficult to discern in a black skin.

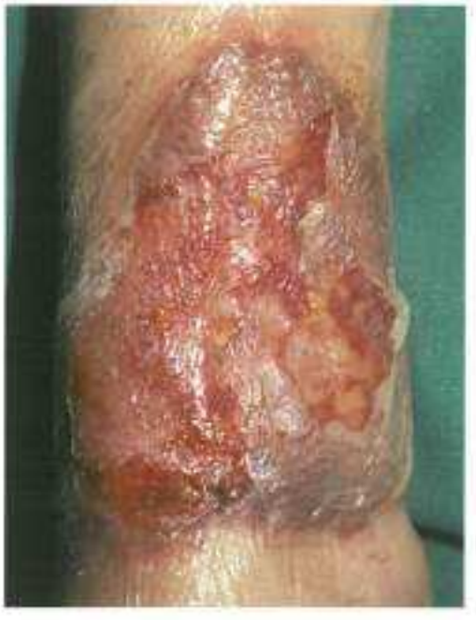


Fig. 23.20 Pyoderma gangrenosum. The ulcer has a bullous and purple surround. His original lesion was misdiagnosed as a necrotizing fasciitis following a dog bite and was debrided. Subsequent lesions at medical intervention sites were mismanaged until a dermatologist was called in. Swabs were negative and systemic steroids cleared it quickly.

foot or toes, which are quite different sites from those of a venous ulcer. Neuropathic changes are also responsible for ulceration (Fig. 23.17), particularly in diabetics.

- **Infections** There is increased incidence of fungus infections, particularly *Trichophyton rubrum*.
- **Blood supply** The pulses are absent or diminished. Severe ischaemia results in gangrene (Fig. 23.18). The toes are usually affected first.

Management

The Doppler ultrasound technique measures the ratio of the ankle-to-brachial systolic pressure, which obviously should normally be 1.0. A ratio of 0.7 or less indicates arterial disease, and the patient requires referral to a vascular surgeon for arteriographic assessment and consideration of thrombolytic or operative techniques, such as lumbar sympathectomy or arterial reconstruction for proximal disease. Associated measures to control diabetes, hypertension, weight and smoking are imperative. Elasticated stockings are contraindicated as they restrict the already compromised blood supply to the leg. Topical remedies are similar to those used for the treatment of venous ulcers but are less effective. Granulocyte-macrophage colony-stimulating factor has been used in diabetics to treat the ulcers. It may heal by upregulating proinflammatory cytokines.

The major differential diagnosis is venous ulceration although both frequently coexist. Arterial ulcers are painful and affect particularly the toes, heels and shins. The skin is dry, shiny, scaly and atrophic. Its colour is pale, cyanotic and there may be a blotchy erythema. The hair is absent. The nails are dystrophic and the pulses are reduced or absent. Venous

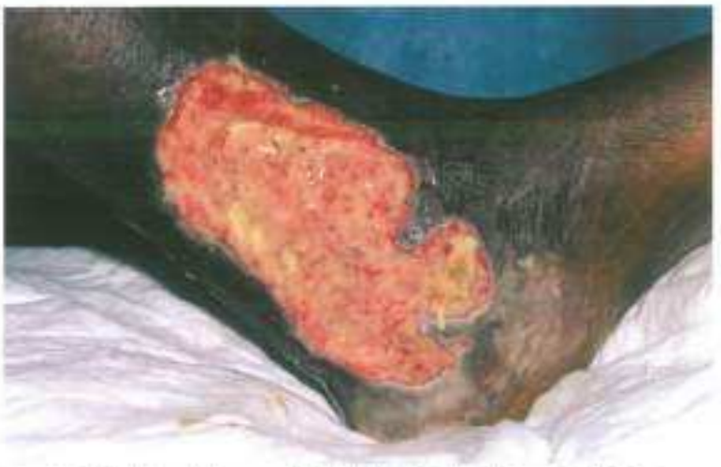


Fig. 23.21 Sickle cell disease. This West Indian girl had no varicosities or venous hypertension to explain her ulcers. They were caused by sickle cell disease.

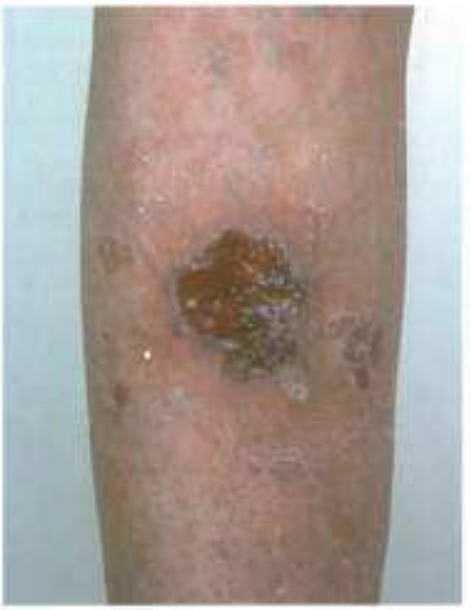


Fig. 23.22 Ulcerated basal cell carcinoma. This ulcer occurred on the back of the leg, an unusual site, for a vascular lesion. The margin of the ulcer is rolled and pigmented.

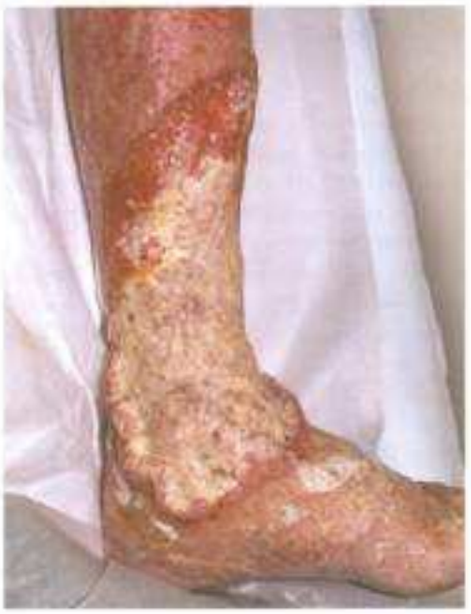


Fig. 23.23 Squamous cell carcinoma. This large ulcer with a purulent base and indurated margin had been misdiagnosed as a varicose ulcer. Biopsy established the correct diagnosis.

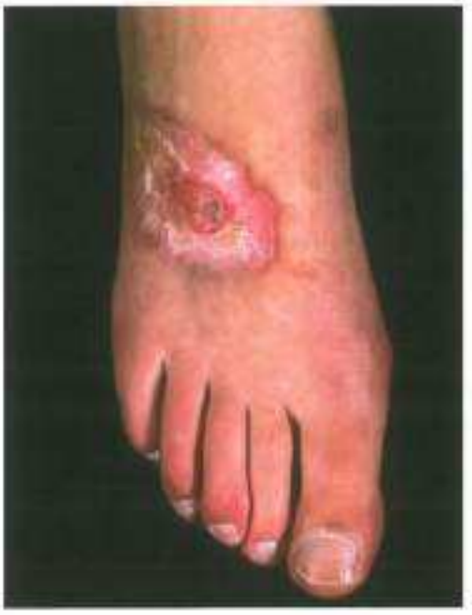


Fig. 23.24 Necrobiosis lipoidica. There is an ulcer within a very well-defined, waxy, yellow-red plaque with a mauve edge. The shins are a classical site.

ulcers are usually not painful and affect the malleoli. There may be eczema and pigmentation but the hair, nails and pulses are normal. Other causes of leg ulcers are:

- **Pyoderma gangrenosum** (Figs 23.19 and 23.20)
- **Dysglobulinaemias**
- **Sickle cell and thalassaemia** (Fig. 23.21)
- **Basal cell carcinoma** (Fig. 23.22)
- **Squamous cell carcinoma** (Fig. 23.23)
- **Klinefelter's syndrome**
- **Erythema induratum**
- **Necrobiosis lipoidica** (Fig. 23.24)
- **Vasculitis** (Fig. 23.25)
- **Pressure sore**

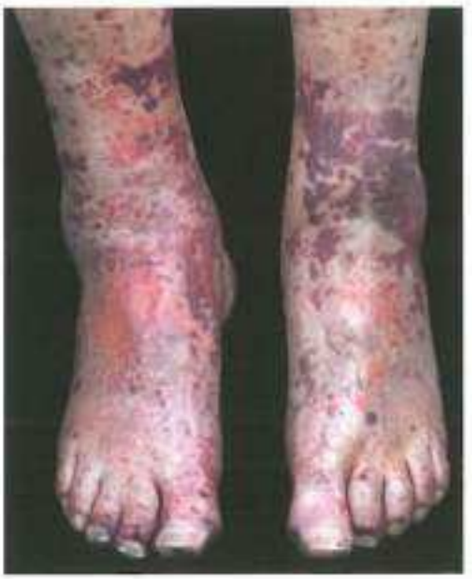


Fig. 23.25 Vasculitis. There is purpura and eroded skin on the dorsum of his feet. His vasculitis was secondary to the immunological dysfunction associated with his myelodysplastic syndrome.

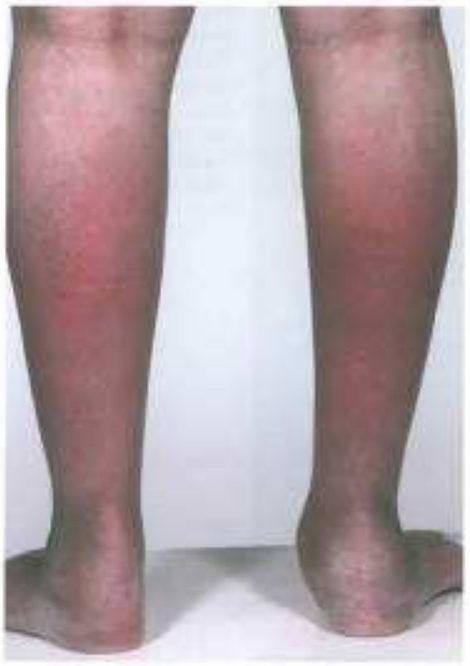


Fig. 23.26 Pergolide-induced retroperitoneal fibrosis. This may occur with Pergolide, an ergot derivative used to stimulate dopamine receptors in Parkinsonism. Erythema and oedema are present.

- **Prolidase deficiency**
- **Epidermolysis bullosa**
- **Pergolide-induced retroperitoneal fibrosis** (Fig. 23.26)
- **Martorell's ulcer.**

Prolidase deficiency is transmitted as an autosomal recessive disorder. It is a rare cause of leg ulceration often starting in childhood and associated with skin fragility. There is a characteristic facies with hypertelorism and a saddle nose and many other abnormalities, but a particular characteristic is that it is unresponsive to treatment.

Martorell's ulcer is usually seen in females secondary to poorly controlled diastolic hypertension. There is severe pain out of proportion to the physical signs. It is due to skin infarction secondary to arteriolar narrowing. There is no venous pigmentation, oedema or evidence of peripheral vascular disease.

Perniosis (Chilblains)

Localized inflammatory lesions of the extremities, induced by cold.

Aetiology

Perniosis is a vasculitis in response to cold that produces an abnormally prolonged vasoconstriction, followed by a reactive hyperaemia. It is now less common in the UK, because of central heating and double glazing. However, some individuals are more predisposed, particularly women, children and immigrants who are unused to the winters of northern climates.

Clinical Features

Symptoms

Very itchy initially and sometimes painful on rewarming.

Morphology

There are crops of dusky red or purple swellings (Fig. 23.27).

Distribution

Chilblains usually occur on peripheral exposed areas, the fingers and toes, and occasionally the nose and ears.

They sometimes occur on the backs of the thighs, especially in overweight young women who horseride wearing damp, tight-fitting jeans.

Differential Diagnosis

The differential diagnosis of painful purpuric lesions on acral sites include:

- **Lupus erythematosus** The perniotic lesions are more pronounced (Fig. 23.28) and necrosis can occur, but there are usually other features of lupus erythematosus, such as cuticular haemorrhages, a skin eruption on light-exposed areas and detectable antinuclear factor.
- **Emboli** Small, cutaneous infarcts of the fingers and toes may result from thrombi associated with endocarditis (Fig. 23.29), valvular disease, myocardial infarction, atrial myxomas, atrial fibrillation or an aneurysm (Fig. 23.30).
- **Blue toe syndrome** (Fig. 23.31) This often follows cardiac catheterization or surgery, particularly in the elderly. There is decreased arterial perfusion from atheromatous or cholesterol crystal emboli in the distal arteries (femoral or popliteral), but occasionally aorti or iliac. Other causes of embolism are cardiac or aortic tumours (myxoma and intimal aortic angiosarcoma) and cardiac vegetations (infective and non-bacterial endocarditis). Thrombosis (antiphospholipid syndrome, paraneoplastic acral vascular syndrome, thrombotic thrombocytopenic

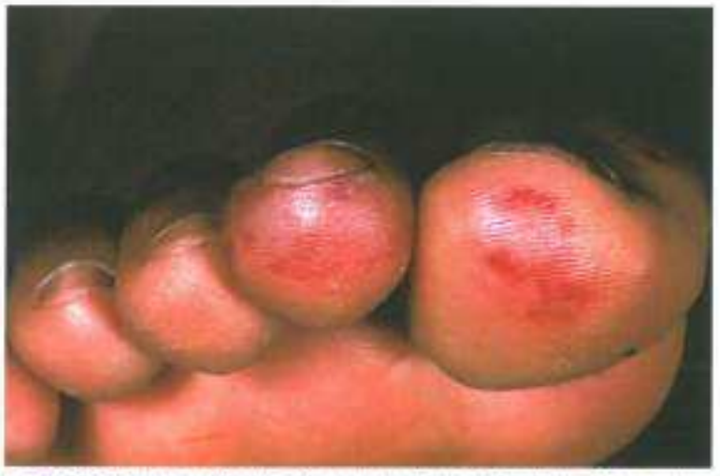


Fig. 23.27 Chilblains. Discrete itchy and sometimes painful dusky red or purple swellings occur on peripheral areas, such as the toes.

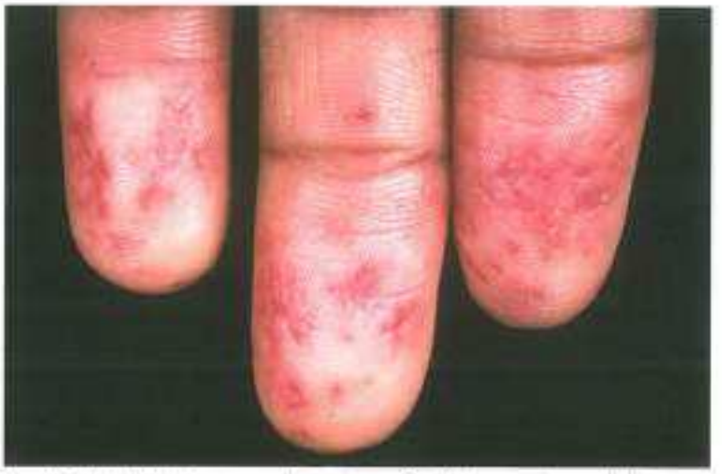


Fig. 23.28 Chilblain lupus erythematosus. Painful deep-red or purple lesions may occur on the fingers in the winter, particularly in women.

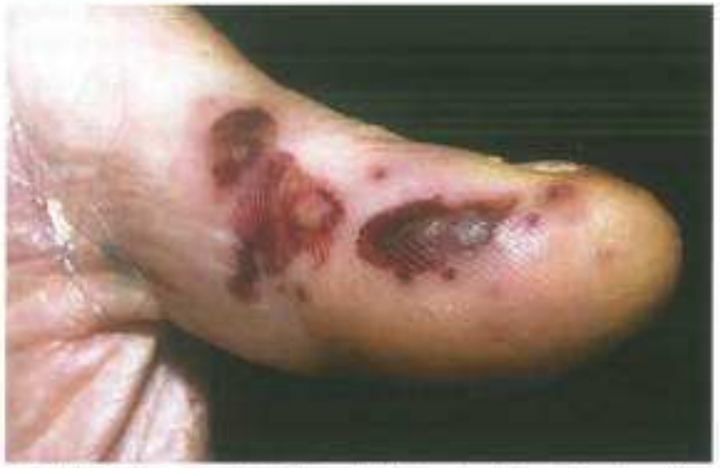


Fig. 23.29 Cutaneous emboli. This patient had subacute bacterial endocarditis and these lesions are secondary to emboli from vegetations on his aortic valve.

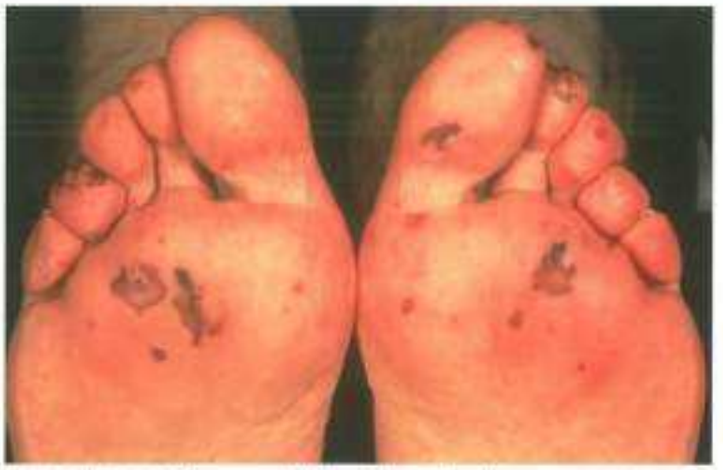


Fig. 23.30 Emboli. There are multiple small areas of cutaneous necrosis. This man was developing emboli from a mural thrombus in an aneurysm of his left ventricle.

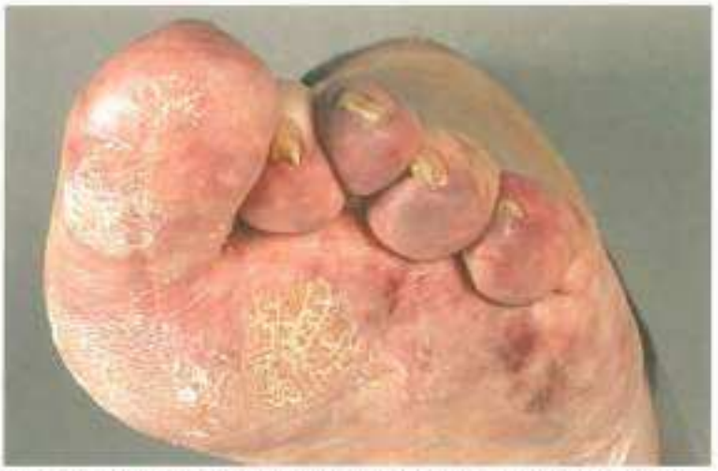


Fig. 23.31 Blue toe syndrome. The toes are blue and there is livedo reticularis on the forefoot. This patient developed gangrene a few weeks later.

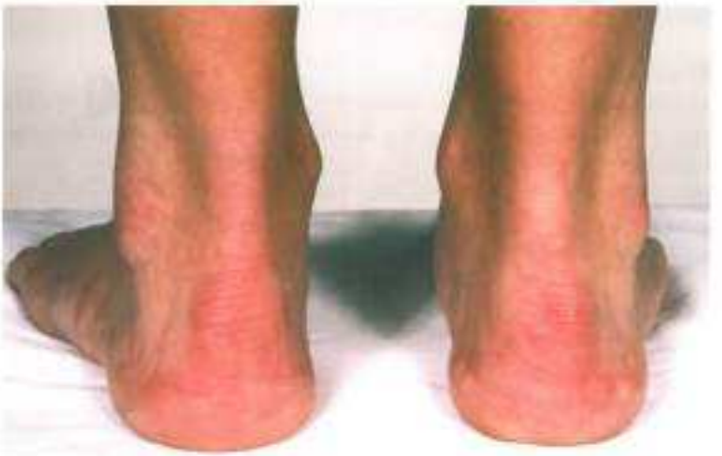


Fig. 23.32 Piezogenic pedal papules. These lesions are not easy to photograph, but the papules can be seen around the right heel of this 11-year-old girl. They are due to herniations of normal fat on standing.

purpura, disseminated intravascular coagulation and warfarin skin necrosis) and vasoconstriction may also cause decreased arterial perfusion. Other causes are impaired venous outflow following extensive thrombosis and abnormal circulating blood components, viz. paraproteinaemia, myeloproliferative disorders, cryofibrinogenaemia, cryoglobulinaemia and cold agglutinins. There are purple toes with painful ulceration and digital gangrene, often associated with livedo reticularis. Cholesterol clefts are found on biopsy and help to make the diagnosis. The kidneys, eyes, gastrointestinal tract and muscles may also be involved.

- **Erythromelalgia** This is precipitated by exercise or warmth and consists of painful, burning, red and vasodilated extremities. It usually occurs secondary to inflammatory or degenerative peripheral vascular disease but may be associated with thrombocythaemia in myeloproliferative disorders. In these patients, the lesions may be unilateral or even affect one digit only and may be relieved by aspirin. There is arteriolar inflammation resulting from platelet-rich thrombi in the end arterial vasculature. The increased platelets may be relieved by aspirin. Venlafaxine may benefit idiopathic cases.
- **Erythermalgia** *Primary erythermalgia* is a condition of intense attacks of warm painful red extremities with insense burning commencing in the first decade, sometimes later. There are mutations in the SCN 9A on chromosome 2q, which encodes Na channel Nav 1.7 and enhances its activation. *Paroxysmal extreme pain disorder* is due to mutations in Nav 1.7, such that inactivation is impaired. There is rectal, periocular and perimandibular pain.
- **Piezogenic pedal papules** These appear on the side of the heels (Fig. 22.32) with the pressure (piezogenic) of standing. They consist of normal fat and are sometimes painful if the fat herniates into the dermis. They are harmless.
- **Gonococcaemia** (Ch. 13).

Management

Basic advice on keeping warm is common sense and essential. Ensuring that the hands and feet are warm well in advance of going out into the cold and wearing fleece-lined or skiing gloves and thermal underwear are all advisable. Central heating at home and at work are helpful, but not always possible, and occupations that involve working outside, or in unheated buildings, make management difficult. Other treatments that have been tried are:

- **ultraviolet light:** three times weekly at the beginning of the winter, sufficient to produce erythema.
- **nifedipine** (10 mg three times daily): this calcium antagonist produces vasodilatation by reducing the vasomotor tone.

Raynaud's phenomenon

Painful, paroxysmal episodes of pallor and coolness of the fingers, and sometimes toes, followed by cyanosis and reactive hyperaemia, most often precipitated by cold.

Aetiology

The exact mechanism is not known. Some incidences are caused by malfunctioning of the sympathetic nervous system, but circulatory catecholamines, abnormalities of blood viscosity, red cell deformity, platelet aggregation or fibrinolysis have been implicated. If there is a known cause then the disorder is known as Raynaud's syndrome; if not, it is referred to as Raynaud's disease. Many patients with chronic disease are later found to have systemic sclerosis. Antinuclear antibodies are often found in older patients and these represent a common subset of incomplete connective tissue disease that may evolve.

Clinical Features

Symptoms

The fingers go white, blue and finally red in response to immersion of the hands into cold water or in cold weather conditions.

Morphology

The pallor results from vasoconstriction (Fig. 23.34), the blue colour is due to subsequent peripheral cyanosis, and the redness to reactive hyperaemia. In severe cases, there may be trophic changes. The skin is tethered and the fingers are tapered (sclerodactyly). The nail plates are thinned and ridged. Gangrene is unusual except in those cases associated with scleroderma.

Distribution

The fingers are affected.

Management

Raynaud's phenomenon is sometimes confused with *acrocyanosis* (Fig. 23.35). This is a term for a persistent discoloration of the hands and feet, occasionally of the nose and ears, as a result of reduced peripheral circulation. The skin appears blue and feels cool or cold. It is common and on the whole gives rise to few symptoms. *Blue finger syndrome* affects a single finger (Fig. 23.36), which goes blue in colour spontaneously periodically, but always returns to normal. The cause is unknown.

The common causes of Raynaud's phenomenon are:

- Connective tissue disorders especially scleroderma
- Occuation, e.g. use of pneumatic drills
- Neurological disease, e.g. cervical rib
- Occlusive arterial disease, Buerger's disease
- Immunoglobluin disorders: cryoglobulinaemia, cold agglutinins
- Toxins: ergotism, heavy metals, vinyl chloride
- Drugs: amphoterin, imipramine, dopamine, noradrenaline and arginine vasopressin.

Common-sense measures should be taken, such as stopping smoking and improving local warmth. Battery-heated gloves may prove useful. Many drug regimens have been tried, including nifedipine and intra-arterial infusion of reserpine, prostaglandin E, prostacyclin and low-molecular-weight dextran. Sympathectomy is worth considering in severe Raynaud's disease. Viagra (sildenafil citrate) may temporarily improve digital flexibility and dexterity in limited systemic sclerosis.

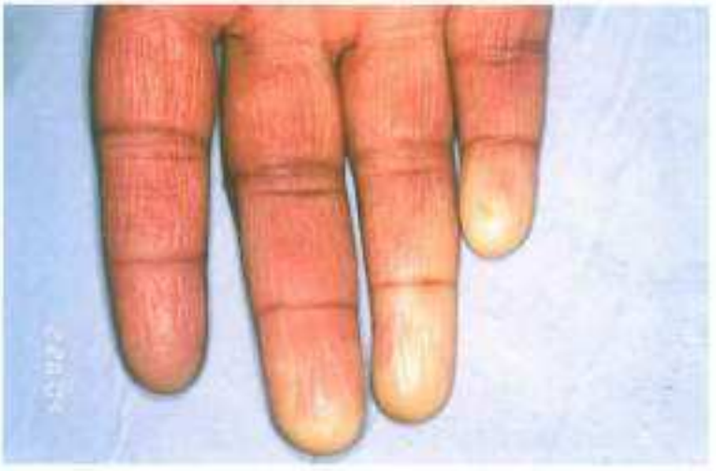


Fig. 23.34 Raynaud's phenomenon. There is pallor of the tip of the index finger, which is noticeable when compared with the middle finger.

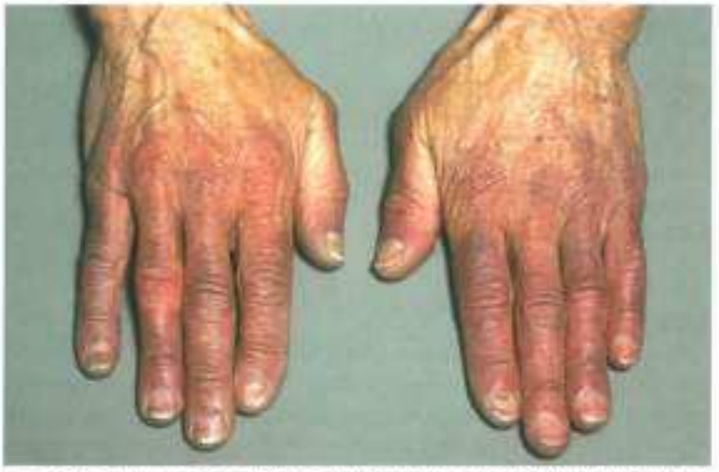


Fig. 23.35 Acrocyanosis. This term is used to describe persistent discoloration of the peripheral skin caused by poor circulation. There is a marked contrast between the colour of the fingers and wrists.

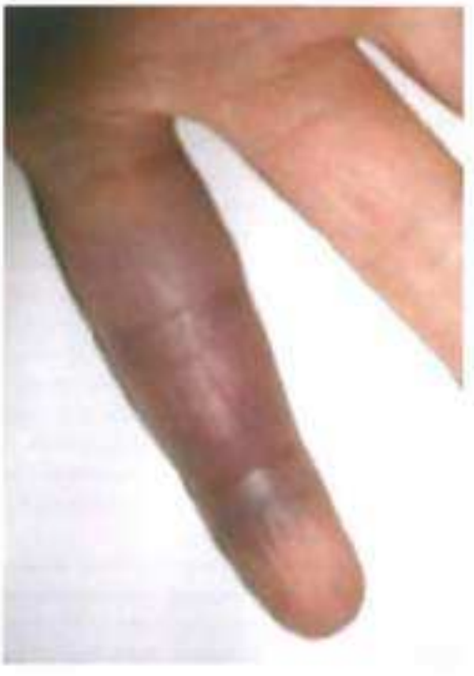


Fig. 23.36 Blue finger syndrome. A single finger rather alarmingly goes a deep purple colour spontaneously. It is not common, but is well described and is quite benign in that the colour returns to normal within a short space of time.

Erythema ab igne

A net-like appearance on the lower legs caused by thermal injury.

Aetiology

The condition highlights the distribution of the blood vessels in the superficial plexus under the skin such that there is a permanent pigmented net-like pattern to be seen in the skin, usually of the lower legs. It particularly occurs in elderly women and myxoedematous patients who sit too close to a fire to keep themselves warm or from the application of a hot water bottle to relieve pain in the abdomen or back.

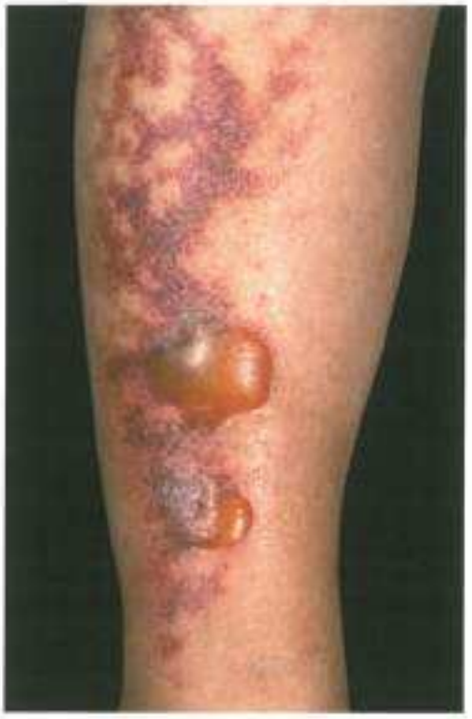


Fig. 23.37 Erythema ab igne. A permanent pigmented net-like pattern results from burns of the skin, in this case from sitting too close to a fire. Actual blisters from a recent burn are present.

Clinical Features

Symptoms

There is a discoloration on the skin.

Morphology

Initially, a reticulate erythema occurs secondary to vasodilatation of the blood vessels in the superficial plexus under the skin; sometimes, this is accompanied by blistering (Fig. 23.37) from superficial burns. Gradually, permanent pigmentation develops. Rarely squamous cell carcinoma results.

Distribution

Usually the lower legs are affected from sitting too close to a fire but the erythema can occur at any site of thermal injury, including a hot water bottle (Fig. 23.38) or on the thighs from prolonged use of a laptop.

Management

Hypothyroidism should be ruled out. Explanation and improvement in heating are needed. The differential diagnosis is of livedo reticularis ([Fig. 23.39] Ch. 18), which affects both legs and often the arms.

Pressure sores

Ulcers secondary to tissue anoxia from prolonged immobilization.

Aetiology

Immobilization, either from unconsciousness or an illness (usually neurological or rheumatological), causes impaired blood supply to the skin and subcutaneous tissues and ulceration (bed sores). Often the patients are elderly, overweight and may be incontinent.

Clinical Features

Symptoms

Usually the ulcers are asymptomatic.

Morphology

Initially, a slight erythema, followed by erosion, ulceration and necrosis.

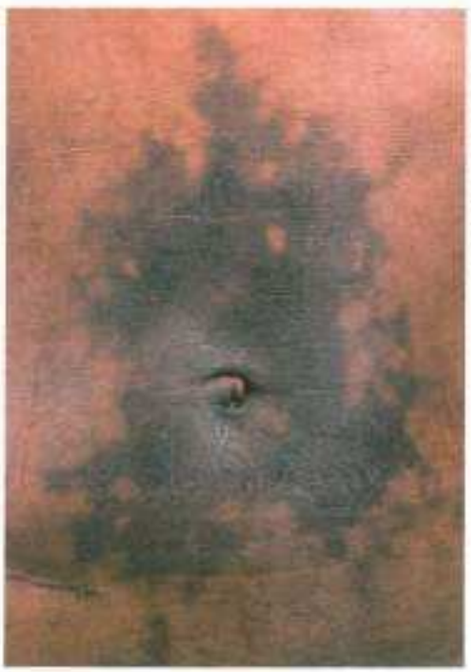


Fig. 23.38 Erythema ab igne. This patient had abdominal pain and attempted to relieve it by putting a hot water bottle next to her skin. A reticulate pigmentation corresponding in distribution to the underlying vascular plexus has resulted.

Fig. 23.39 Cryoglobulinaemia. Livedo reticularis and purpura occur in association with cold-induced cryoglobulins and in this case hepatitis B.

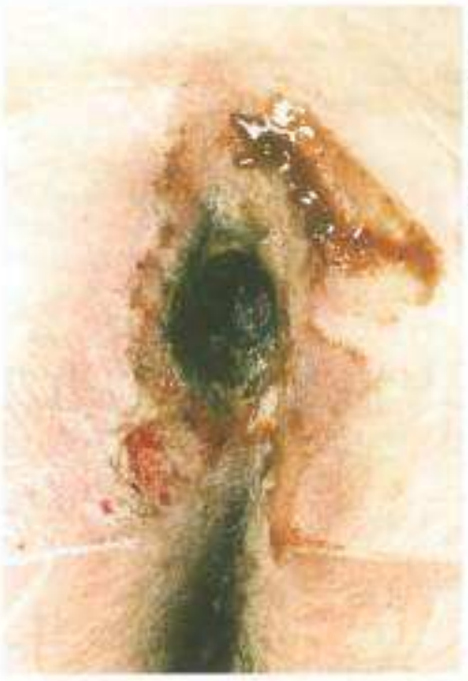


Fig. 23.40 Neuropathic ulcer. This patient has disseminated sclerosis and no sacral sensation. The ulcer has developed partly because of this, in addition to prolonged pressure and incontinence.

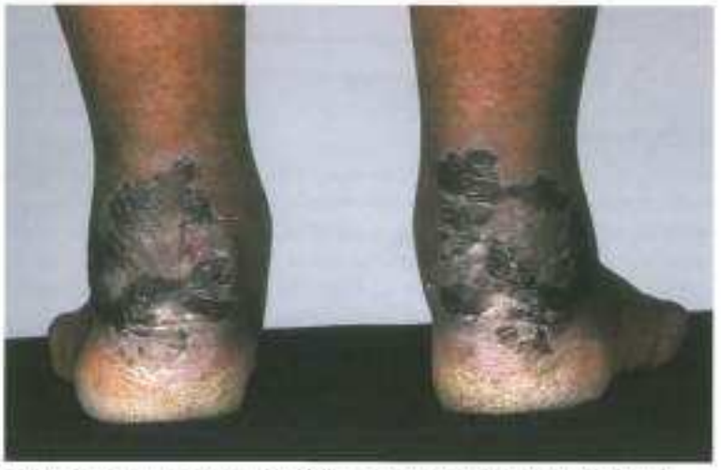


Fig. 23.41 Pressure sore. The heels became ischaemic because this young woman was immobile from a barbiturate overdose. Necrosis and ulceration of the skin are present.

Distribution
The ulcers occur at pressure points: the sacrum (Fig. 23.40), scapulae, backs of the heels (Fig. 23.41) and scalp.

Management
Bed sores are difficult to heal; therefore, prevention is paramount. Any patient admitted to hospital who is unable or unwilling to shift his or her position in bed is a candidate. It is imperative that the patient is turned and moved at least every 2 hours. In many cases, however, the process has already started before the patient is admitted.

Deckchair legs

Deckchair legs is a common condition of the lower leg resulting from prolonged immobilization.

Aetiology
The condition gained its nickname from its description in those rendered homeless in London during the blitz in World War II, who passed the night sleeping in deckchairs in the Underground. It occurs now in immobile or debilitated patients who lead an armchair existence and sleep in a chair rather than in a bed at night. The lymphatic and venous return is consequently always working against gravity, resulting in oedema and erythema, possibly as a result of low-grade cellulitis.

Clinical Features
Symptoms
There is swelling of the legs.

Morphology
There is erythema and oedema, and blistering may occur in extreme cases (Fig. 23.33). The skin is quite cool on examination, unlike in cellulitis.

Distribution
The lower limbs are affected.

Management
Restoration to a healthier, more active life may bring with it recovery, but this is frequently difficult because of accompanying general debility.

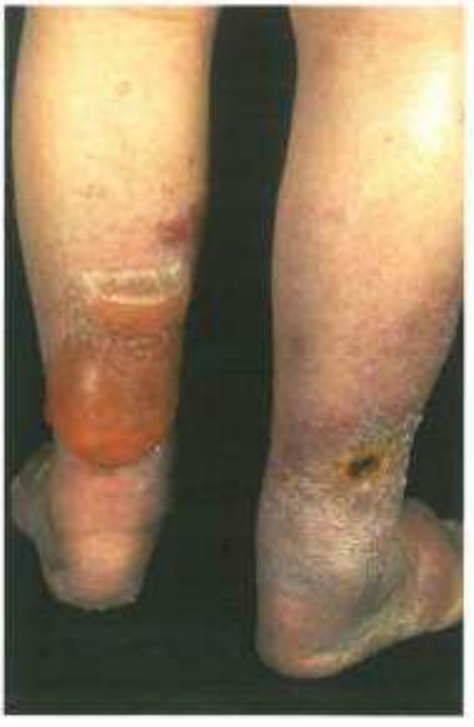


Fig. 23.33 Deckchair legs. Prolonged immobilization with the legs dependent results in oedema and erythema, often with blistering. It is common in those who lead an armchair existence.

Arteriovenous malformations and fistulae

Arteriovenous fistulae are direct connections between an artery and a vein, which may be congenital or traumatic in origin.

Aetiology

Congenital lesions are present at birth but often as a faint ill-defined erythema, which becomes detectable during expansion in puberty. They may be multiple and other abnormalities, for example capillary lymphaticovenous malformations (*Klippel–Trenaunay syndrome*) may be present. Acquired fistulae are the result of a penetrating injury.

Clinical Features

Symptoms

The area is warm, may be pulsatile and painful.

Morphology

The degree of abnormality depends upon the size of the fistula and volume of abnormal blood flow. It amasses a deep erythematous or violaceous colour and ulceration is usually present (Fig. 23.42). A thrill may be elicited on palpation and a bruit on auscultation. Venous insufficiency distal to the fistula is usual. Indeed unilateral venous insufficiency in a young person (Fig. 23.43) without a family history might suggest the diagnosis. In large fistulae, cardiac decompensation may result.

Distribution

They may occur anywhere.

Management

Doppler studies and arteriography should confirm the diagnosis. Surgery is indicated.

Lymphoedema

A non-pitting tissue swelling secondary to failure of lymphatic drainage in the presence of normal capillary filtration.

Aetiology

Oedema is the result of an imbalance between capillary filtration and lymphatic drainage. Most forms (cardiac, hepatic or renal) are the result of increased capillary filtration overwhelming the lymphatic drainage. In lymphoedema, capillary filtration is normal but the lymphatics do not drain satisfactorily. There are two types of lymphatic vessels: large collecting vessels, which contain smooth muscle, and smaller ones that drain passively but respond to intermittent muscular contractions with movement, arterial pulsations and local massage. They drain excess fluid, cells, protein, lipids, microorganisms and debris from the tissues. Limb lymphoedema is the commonest presentation. Midline lymphoedema is less common because there is bilateral crossover of lymphatic drainage.

The causes are primary, which is usually the result of an underdevelopment of the lymphatics but may be associated with Turner's or Noonan's syndrome or be part of a widespread vascular abnormality, such as the Klippel–Trenaunay syndrome. Secondary lymphoedema may follow surgical removal of lymph nodes, radiotherapy (it is not known why some patients do develop lymphoedema and others do not), infection (including filariasis) sirolimus in patients with renal failure and in association with chronic venous disease (particularly if ulceration is present).

Primary lymphoedema of the limb may be present around birth, at puberty (praecox) or at the menopause (tarda). These are non-familial and are the most common. Familial lymphoedema (Milroy's at birth and Meige's in childhood) is rare. Mutations in the lymphatic receptor 3 (VEGF receptor 3) affect two key growth factors (VEGF C and D), which control

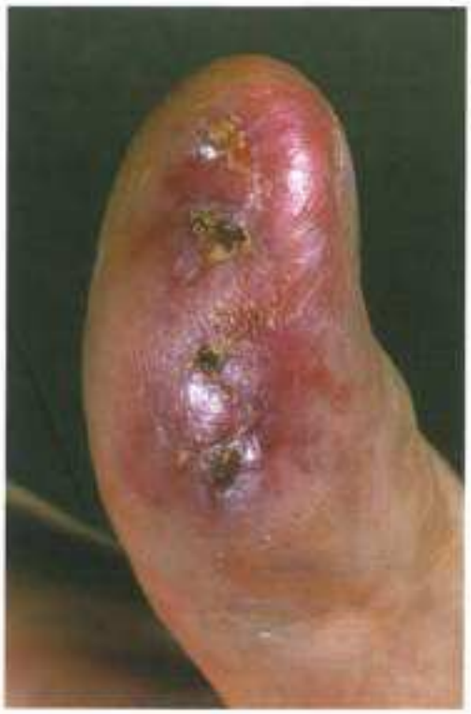


Fig. 23.42
Arteriovenous fistula. The thumb was purple, painful and enlarging. Ulceration was present.

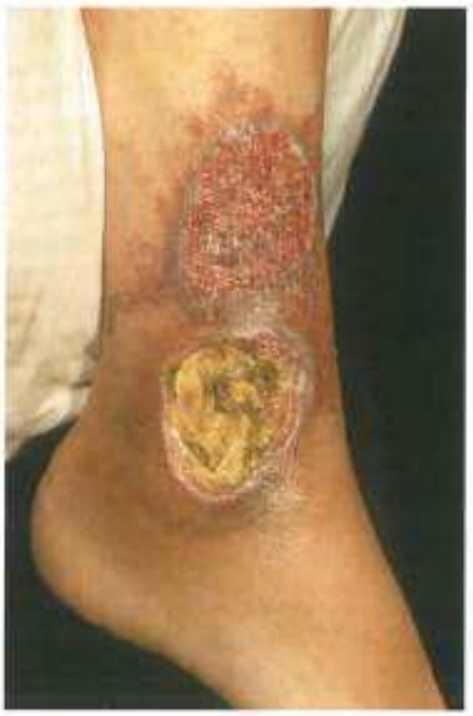


Fig. 23.43
Arteriovenous fistula. The unilateral nature of the ulceration and the age of the patient (12 years old) were suggestive of the diagnosis.

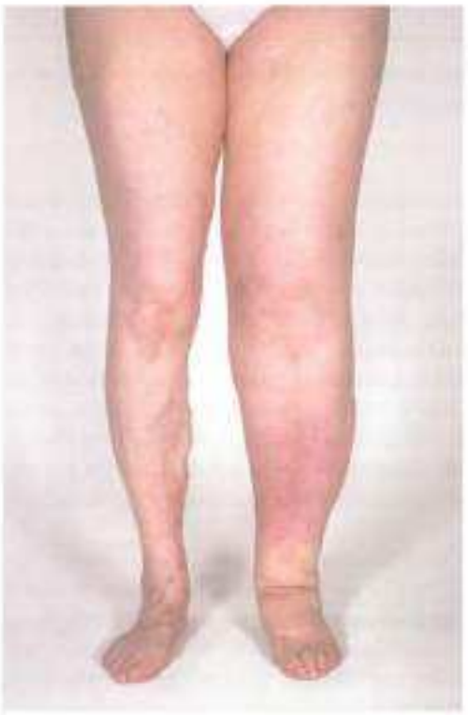


Fig. 23.44 Primary lymphoedema. The patient's left leg is grossly swollen as a result of congenital lymphatic hypoplasia.

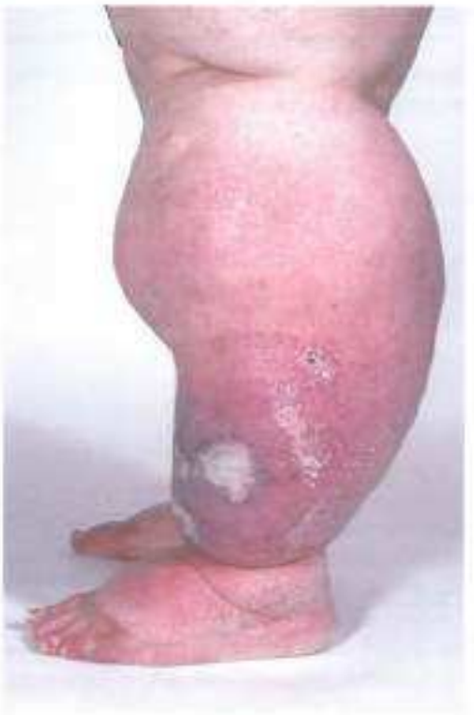


Fig. 23.45 Primary lymphoedema. The lymphoedema began after puberty. The skin is oedematous and initially does not pit. The feet may be quite normal. Recurrent cellulitis is common.

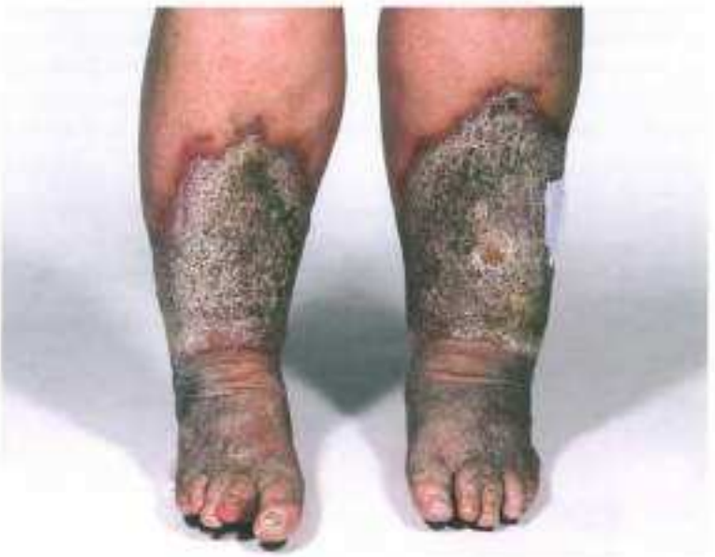


Fig. 23.46 Primary lymphoedema. Gradually hyperkeratosis, papillomatosis and fibrosis develop, producing a warty elephant-like skin.

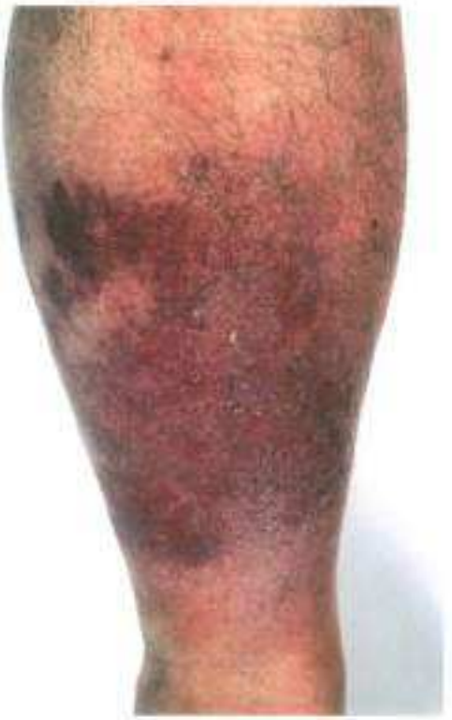


Fig. 23.47 Cellulitis. Fever, toxicity (nausea, debility and sometimes confusion) accompany discomfort, redness and oedema of the leg. These patients frequently have underlying lymphatic insufficiency, which renders them susceptible to recurrent attacks.

lymphatic survival, proliferation and migration and are responsible for primary congenital lymphoedema. Both sexes may be affected. Mutations in Forkhead family transcription factor C2 is responsible for Meig's late onset lymphoedema.

Midline lymphoedema is usually secondary but if there is primary facial lymphoedema it is usually part of a widespread congenital problem. Secondary periorbital lymphoedema occurs with rosacea. Other causes include dermatomyositis, thyroid disease, the yellow nail syndrome, or following contact dermatitis or erysipelas. Lymphoedema of the upper or lower lip, or both, may occur initially intermittently and subsequently become permanent. If granulomas are present, the condition is known as orofacial granulomatosis (*Melkerson–Rosenthal syndrome*), the cause of which is unknown. Occasionally it is associated with Crohn's disease or sarcoidosis.

External genital and leg lymphoedema is usually secondary to obstruction from pelvic or abdominal carcinoma. However, primary lymphatic deficiency of the penis and scrotum or mons pubis does occur and is frequently complicated by recurrent cellulitis.

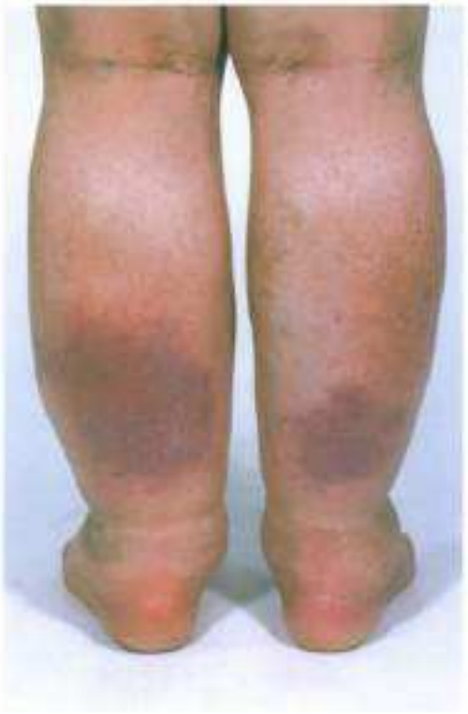


Fig. 23.48 Primary lymphoedema. Both legs may be affected. The feet, by contrast, appear comparatively normal.

Fig. 23.49 Lipoedema. There is bilateral deposition of fat with chunky thighs and legs in stark contrast to a normal torso. (Courtesy of Prof. Peter Mortimer.)

Clinical Features of Limb Lymphoedema

Symptoms

The area feels heavy and uncomfortable as well as being psychologically traumatic.

Morphology

The skin is oedematous (Fig. 23.44), becomes brawny (Fig. 23.45) and does not pit. It is thicker and the skin creases are pronounced. One cannot pinch or pick up the fold of skin at the base of the second toe (Kaposi–Stemmer sign). Hyperkeratosis, papillomatosis and fibrosis (elephantiasis) develop, producing a mossy foot (Fig. 23.46) with lymphangiomas on the surface. Secondary infection with cellulitis (Fig. 23.47) is common but occasionally malignancy may occur, particularly after carcinoma of the breast (*Stewart–Treves lymphangiosarcoma*).

Distribution

One or both legs may be affected (Fig. 23.48).

Management

Unlike other forms of oedema, lymphoedema does not respond to elevation and diuretics and the diagnosis is not difficult. Stemmer's sign is positive. The differential diagnosis includes *lipoedema*, a bilateral enlargement of the legs due to the abnormal deposition of subcutaneous fat associated with oedema (usually mild). It only occurs in females, the Stemmer sign is negative and the feet are normal. 40% have a positive family history. It occurs at puberty resulting in an hourglass figure with chunky legs and thighs (Fig. 23.49). The skin is soft and not thickened but bruises easily. It is chronic and progressive and morbidity (discomfort, pain, limited mobility and knee damage) is considerable. Weight reduction and manual lymphatic drainage have limited effect. Liposuction may be helpful. Immobility in *'the armchair leg syndrome'* results in minimal lymphatic drainage, which is made worse by the increased capillary filtration from the dependent limbs. The lymphatics are quite normal.

There is no effective treatment for primary lymphoedema, although massage and appropriate hosiery are helpful. Lymphoscintigraphy has replaced lymphography for establishing the diagnosis. Labelled colloid is injected into the first web space of the limb and the drainage is measured with a gamma camera. Surgical treatments (debulking or microvascular) are not very successful. Prevention of secondary infection with long-term, low-dose penicillin or erythromycin, however, is very helpful. Exercise and massage is the only effective treatment for midline lymphoedema. Facial, genital and oral lymphoedema are dealt with elsewhere.

Disorders of the sebaceous, sweat and apocrine glands

24

Diseases of the sebaceous gland

Sebaceous glands are found throughout the skin, except the palms and soles, and are under androgen control. They do not secrete until puberty, apart from temporarily during infancy, probably caused by adrenal stimulation. They are at their largest on the scalp, face, neck and the trunk, where they occur in association with hair follicles and share with them a common channel to the surface of the skin, known as the pilosebaceous duct. Sebaceous glands do occur on their own (e.g. the meibomian gland in the eyelid) and in many are visible on the buccal mucous membranes (Fig. 24.1) and on the lips (Fig. 24.2), where they are known as Fordyce spots. Animals require the gland for waterproofing of their fur, but during the course of evolution it has become something of an inconvenient appendage, like the appendix. Certainly, children flourish without active glands.

ACNE

A chronic androgen-dependent disorder of the pilosebaceous apparatus resulting in greasiness and a polymorphic eruption on the face and torso.

Aetiology

Acne (Fig. 24.3) results from overactivity of the sebaceous gland and a blockage in its duct. Androgens and other mediators (insulin growth-like factor, peroxisone proliferator-activated receptor agonists and melanocortins) control the rate of production and composition of sebum.

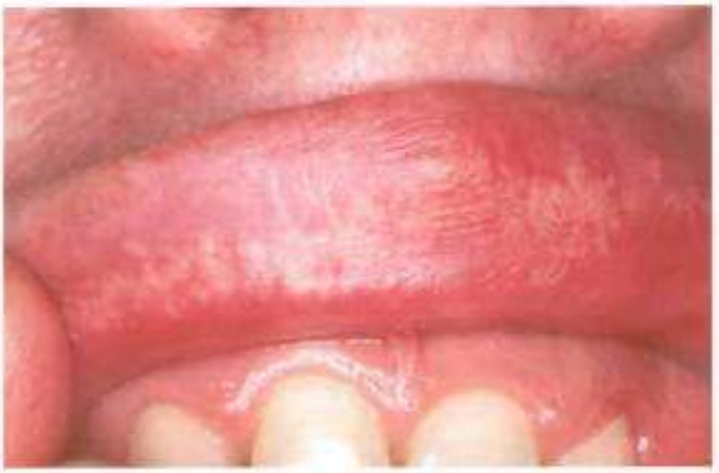


Fig. 24.2 Fordyce spots. Small yellow papules are present on the lips. They are a common normal variant. Patients sometimes worry about them.

Sebum

Sebum secretion is increased in acne and in general the more severe the acne, the greater the production of sebum. However, acne is not a feature of other greasy states such as acromegaly (in which growth hormone increases the production of sebum) or Parkinson's disease (mechanism unknown). In addition, acne vulgaris usually remits in the early twenties, and yet sebum excretion does not fall precipitously at that time.

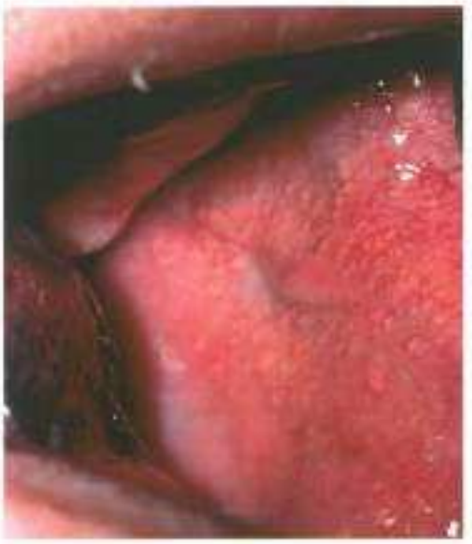


Fig. 24.1 Fordyce spots. Small yellow papules are present on the buccal mucous membrane. They represent sebaceous glands.

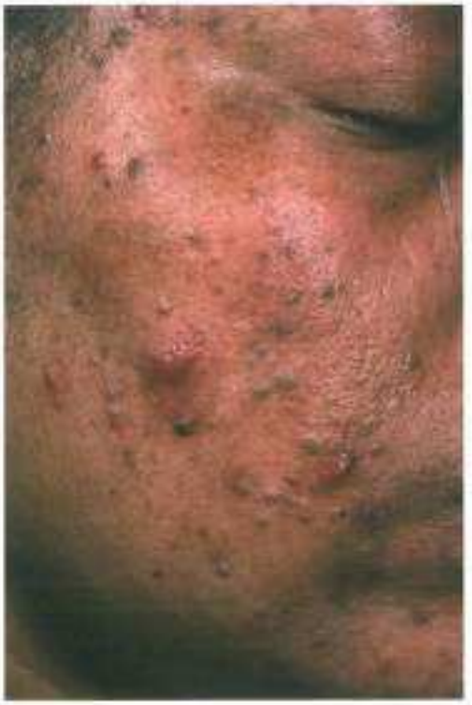


Fig. 24.3 Acne vulgaris. Greasiness, papules and pustules are the common physical signs of acne on the face. It is an androgen-dependent disorder of pilosebaceous follicles, which are activated asynchronously from the menarche until the end of puberty.

Fig. 24.4 Acne vulgaris. The comedone is a blockage of the pilosebaceous duct by a keratin plug. It has ruptured, causing an intense neutrophil inflammatory cell response.

The pustules of acne represent a collection of sebum and are quite sterile. Sebum is formed from the sebaceous gland by a holocrine process, that is the cells of the gland are broken down and converted into lipids: (glycerides, free fatty acids, wax esters, squalene, cholesterol and its esters). Sebaceous glands, like other epidermal structures, are manufactured continuously and probably take a month to reach maturity. This may explain why therapy takes this length of time to act. Free fatty acids (the breakdown products of sebum) are irritants and comedogenic. If injected into the skin, they produce a sterile inflammatory response of polymorphs and lymphocytes, which is what happens when sebum leaks into the skin surrounding the gland. The function of sebum is unclear. It is known to be fungistatic and this is probably why ringworm of the scalp is rare after puberty whereas the yeast of pityriasis versicolor, which is lipophilic, flourishes on sebum and is common after adolescence.

Plugging of the pilosebaceous canal

The comedone or blackhead is one of the initial abnormalities. It is a keratin plug (Fig. 24.4) produced by a failure of the epidermal lining of the pilosebaceous duct to keratinize properly; as a result, the keratinous squames adhere to one another and, together with sebum and bacteria, block and distend the gland. Certain substances aid the formation of comedones, such as free fatty acids, industrial oils, hair pomades and brilliantines. If the blockage is superficial, red papules and pustules result. If it is deeper, larger painful papules, nodules, cysts and scarring may occur.

Microbiology

Acne is not infectious and cannot be transmitted from one subject to another. The pilosebaceous duct and the skin surface are, however, colonized by important microorganisms – *Propionibacteria acnes*, *Staphylococcus epidermidis* and the yeast *Pityrosporon ovale* – of which *P. acnes* is dominant. *Propionibacteria* are lipid-dependent gram-positive anaerobic rods. They are not involved in either comedogenesis or the initial activation of the immune response, but do generate inflammation by upregulating pro-inflammatory mediators (IL-1α, IL-8 and TNF-α) by keratinocytes, leucocytes and sebocytes via toll-like receptor-dependent and independent mechanisms. Although their absolute numbers do not correlate with the severity of the acne, treatments that reduce them improve the disease.

Hormones

The sebaceous glands are directly under hormonal control.

- **Androgens** These are the most important. Sebum excretion at birth is similar to that of adults, but in the period following infancy and through to adolescence, the sebaceous glands are minute and sebum excretion is very low. Acne begins at puberty and is the first sign of pubertal maturation in girls, preceding pubic hair and areola development, and is associated with increased levels of dehydroepiandrosterone sulphate. Consequently, adrenal androgens are important and early acne is a marker of the adrenarche, which precedes the menarche. Adrenal androgens are, however, less potent than testosterone, which also increases sebaceous gland size and increases sebum production. Indeed, eunuchs do not develop acne at all unless they are given testosterone. However, it is not known why acne goes into remission after adolescence, even though testosterone levels remain the same. It may be that there is target organ overactivity, resulting in increased conversion of testosterone to the more potent dihydrotestosterone by the enzyme 5α-reductase at the androgen receptor of the sebaceous gland. Certainly, there does not seem to be any evidence, in males at any rate, that there is an increased output of testosterone, in that all males are maximally stimulated already. In females, however, studies are conflicting. Target organ overactivity may be the key. Alternatively, it has been shown in some women that sex hormone-binding globulin is reduced and, consequently, levels of unbound sex hormones are elevated in serum, and this may be responsible. It is not known why the binding globulin should be reduced, or why all the sebaceous glands are not affected by the increased androgen activity at any one time, instead of just a number being affected. Thus acne is a disorder of androgen metabolism and in women, can be a presentation of a virilizing disease, albeit rarely, in which case other signs of virilization will be present.
- **Oestrogens** The size of the sebaceous gland is reduced by oestrogen. However, high doses, such as 50 mg ethinylestradiol daily, are required to produce a therapeutic effect.
- **Progesterone** This causes water retention with consequent swelling of the epidermis and blockage of the pilosebaceous ducts. Therefore, many mature women note that their acne is worse premenstrually.
- **Thyroxine** The sebaceous glands are stimulated by thyroxine; dry skin is a feature of hypothyroidism.

Mediators of inflammation

The cause of the inflammatory reaction is unknown. It was believed that lipases released from *P. acnes* acted on sebaceous triglycerides to release irritant free fatty acids. However, it seems more likely that *P. acnes* elaborates a low-molecular-weight peptide, an extracellular factor that penetrates the follicular wall, attracts polymorphonuclear leucocytes to the intact microcomedones and initiates inflammation. *P. acnes* is also a potent activator of complement via the classical pathway once *P. acnes* antigens are complexed with their specific antibodies. Activation releases neutrophil hydrolytic enzymes that rupture the follicular wall. Other exoenzymes produced from *P. acnes* may also contribute to its rupture. Once the follicular wall is damaged, various agents – prostaglandin-like substances, amino acids, short-chain fatty acids and lipases – are produced by inflammatory cells and *P. acnes*. These are extruded into the dermis, causing more inflammation.

Clinical Features

Symptoms

Disfigurement.

Morphology

There is greasiness, comedones (Fig. 24.5) both open ('blackheads') and closed ('whiteheads'), milia (Fig. 24.6), red papules and pustules, with sometimes nodules, cysts, scarring (Fig. 24.7), keloids and postinflammatory hyperpigmentation. The cysts are caused by follicular retention. If the cyst opens directly to the surface, pigmented keratin is seen and it is known as a blackhead. If the ostial canal is blocked, a small white papule (or whitehead) results.

Fig. 24.5 Acne vulgaris. Comedones (blackheads) are plugs of keratin that block the pilosebaceous canal. They are a common feature of acne, particularly in early adolescence.

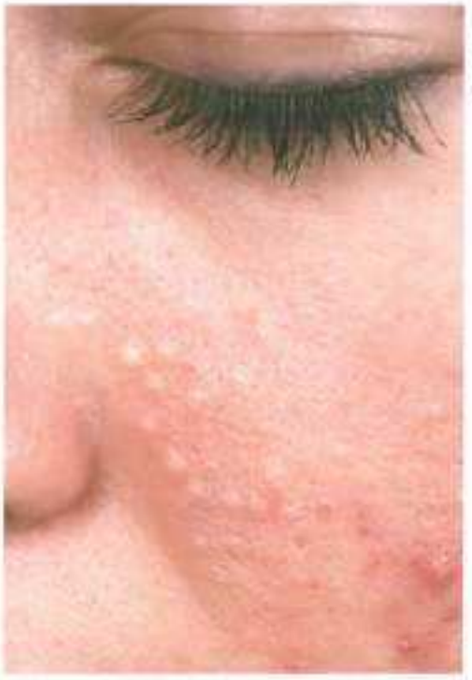


Fig. 24.6 Acne vulgaris. Milia are mini-epidermoid cysts and are frequently associated with acne.

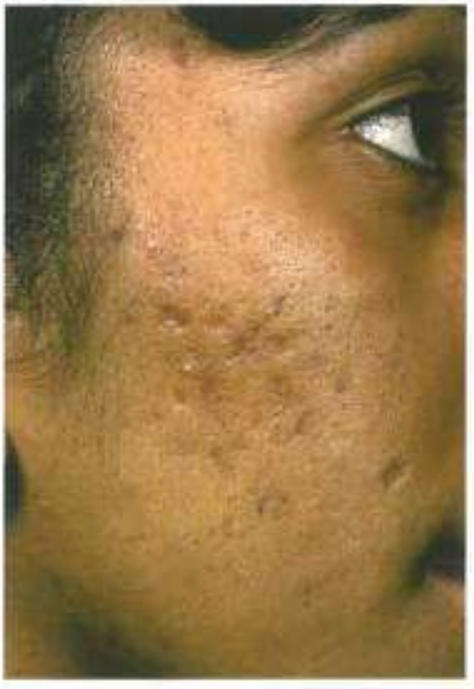


Fig. 24.7 Acne vulgaris. Scarring occurs in some individuals and is permanent.

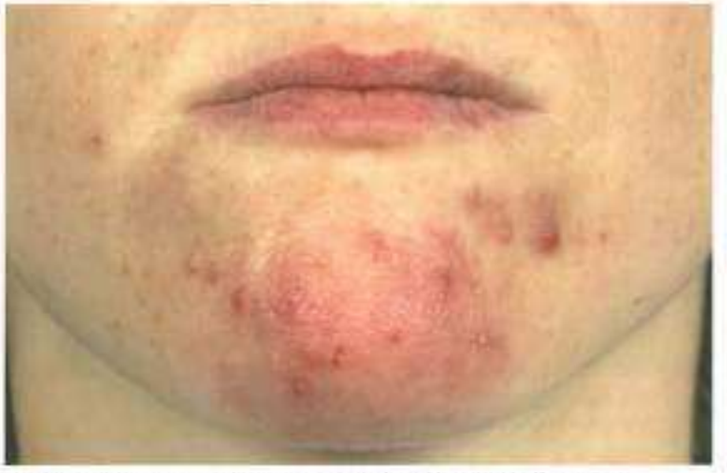


Fig. 24.8 Postadolescent female acne. Papules and pustules occur, particularly on the chin, cheeks and jaw, which may be deep and painful and worse premenstrually. (Courtesy of Dr Michèle Clement.)

Distribution

Primarily on the face and trunk.

Clinical forms of acne

- **Acne vulgaris** This is the commonest and one of the first manifestations of adolescence. It is commencing much earlier than previously; consequently, comedones and milia are quite usual in a 10-year-old child. The disorder reaches maximum activity at 16–18 years and then subsides, but often it does not disappear until the early or mid-twenties. The disorder is almost universal to some degree during adolescence, so that in some it is physiological and can be ignored, whereas in others it requires active treatment. Acne is slightly more common in the teens in males than in females. Early-onset acne has a less good prognosis. About 8% of patients go on having trouble with their acne into their thirties.
- **Postadolescent mature female's acne** This is common in women in their twenties and thirties, who often state that they were not troubled by acne in adolescence. The condition usually clears by the middle or late thirties, but not always. It is clinically different in that it has a predilection for the muzzle area of the chin (Fig. 24.8) and jaw (the equivalent of the beard area in males) and may result in painful deeper lesions, especially premenstrually. Most have low levels of sex hormone-binding globulin and the consequent rise in free, circulating testosterone levels is responsible for the acne. Some have features of the polycystic ovary syndrome. Some relate occurrences to their oral contraceptive, while others have never taken the pill. The more androgenic progestogen-containing pills (levonorgestrel and ethynodiol) probably aggravate it, whereas the minimally androgenic progestogens (desogestrel and gestodene), combined with ethinylestradiol, may be beneficial.

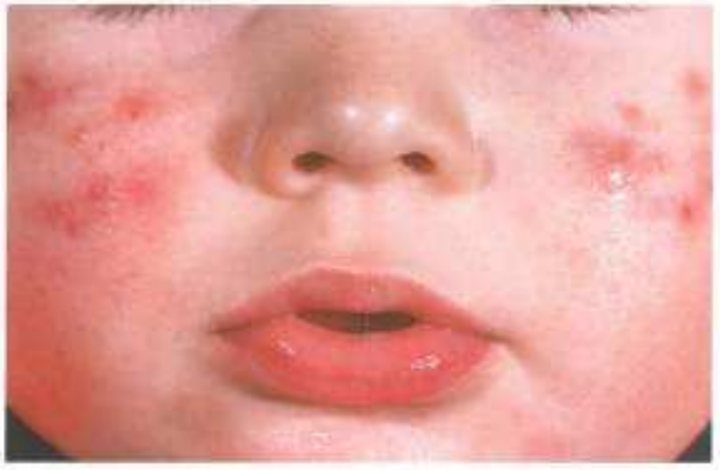


Fig. 24.9 Infantile acne (milk spots). Transplacental maternal adrenal androgens stimulate the infantile sebaceous glands and produce acne. It disappears spontaneously within 3 to 6 months.

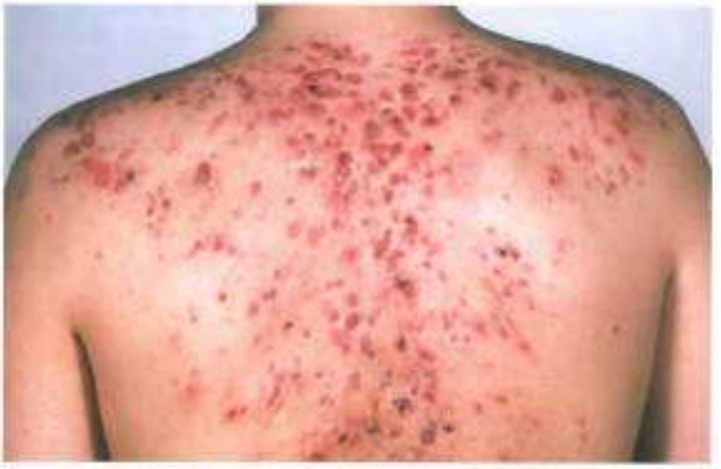


Fig. 24.10 Nodulocystic acne. This is the most aggressive form of acne and 13-cis-retinoic acid is the only effective remedy, although in this case it would be too late to prevent scarring.

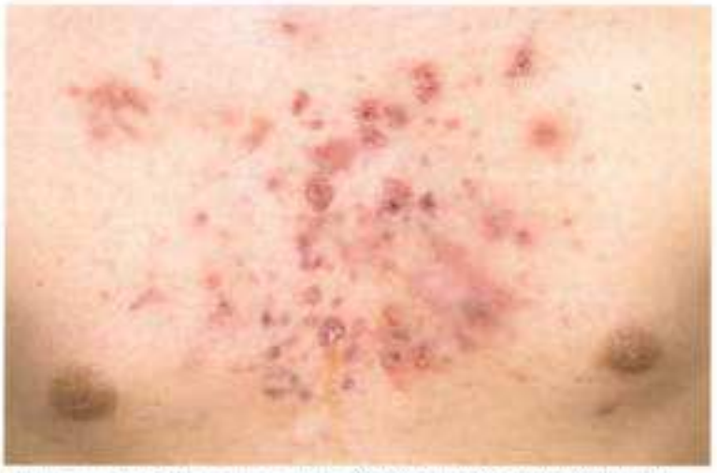


Fig. 24.11 Nodulocystic acne. Large, inflamed nodules, cysts and scarring occur. Isotretinoin has revolutionized treatment.

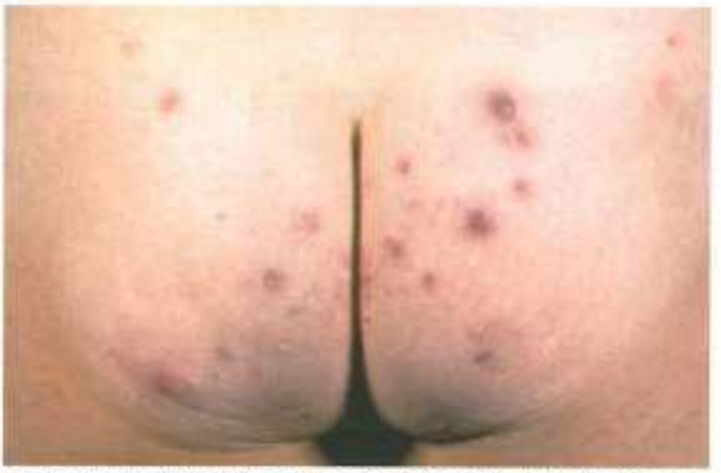


Fig. 24.12 Acne. The buttocks may occasionally be involved without evidence of the disease elsewhere.

- **Infantile acne (milk spots)** The newborn displays endocrine behaviour not unlike that of puberty. Acne, therefore, is quite common in early infancy and may be caused by transplacental stimulation of the sebaceous glands by adrenal androgens rather than by transfer of maternal androgens via breast milk. It occurs predominantly on the cheeks (Fig. 24.9) and passes after a few months. It is occasionally nodular and may result in scarring. Very occasionally, it is a presenting feature of a virilizing tumour or congenital adrenal hyperplasia. Treatment with systemic erythromycin or occasionally 13-cis-retinoic acid is sometimes necessary.
- **Nodulocystic acne** This unpleasant form differs from acne vulgaris in the severity of physical signs, its chronicity and its relative resistance to antibiotics. It occurs in both sexes, but probably more frequently in males. There are deep painful papules and nodules and disfiguring scarring (Fig. 24.10). It usually persists into early middle age. The face, chest (Fig. 24.11) and back may be affected in isolation or together. The buttocks may also be involved (Fig. 24.12). Keloid formation (Fig. 24.13) may occur. Treatment has been revolutionized by isotretinoin (13-*cis*-retinoic acid).

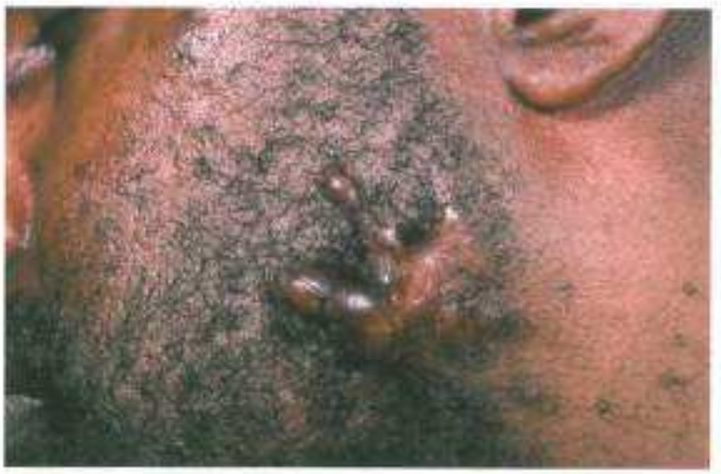


Fig. 24.13 Keloid scarring. This is a major problem in black-skinned patients with either acne (which may not be widespread) or pseudofolliculitis.

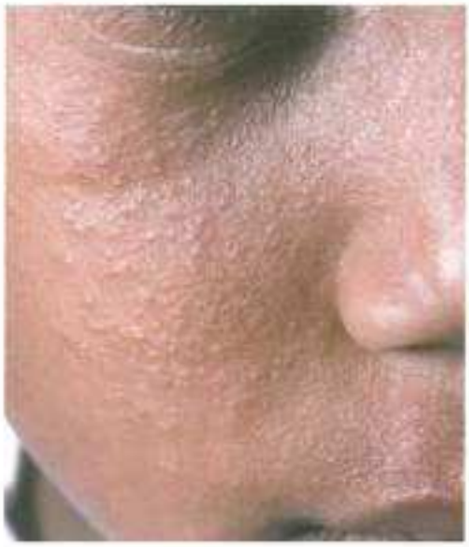


Fig. 24.14 Facial Afro-Caribbean childhood eruption (FACE). This child has an acneiform eruption and yet is only 4 years old. It is not uncommon in Afro-Caribbeans. It responds to oral erythromycin.

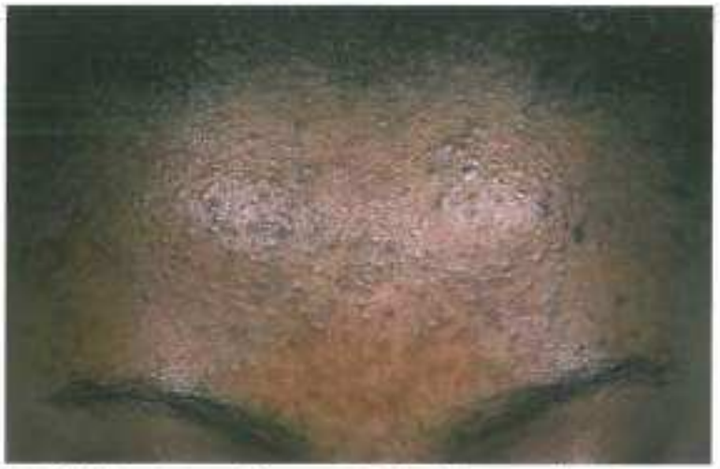


Fig. 24.15 Pomade acne. Greases used for the hair may spread onto the forehead and occlude the pilosebaceous orifices. This is common in black-skinned races.

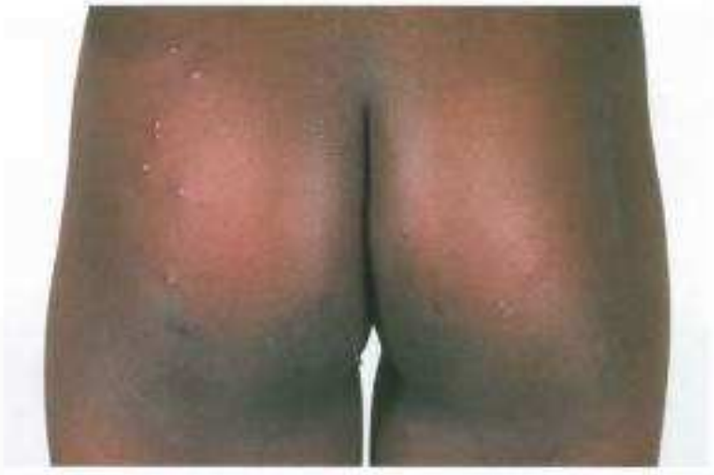


Fig. 24.16 Dermatitis cruris pustulosa et atrophicans. The application of oils to black skin may result in a pustular eruption, which subsequently becomes atrophic.

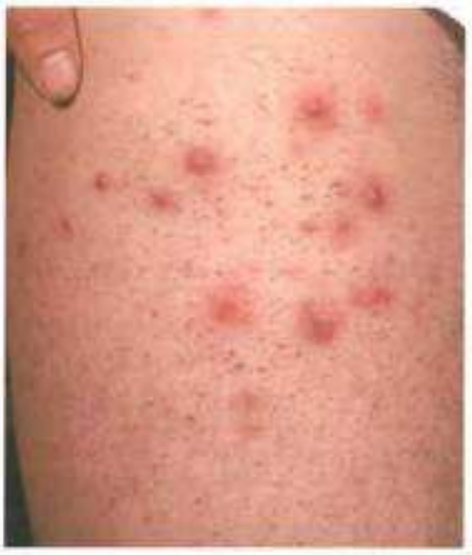


Fig. 24.17 Folliculitis caused by oils. Sterile acneiform papules and pustules develop secondary to follicular occlusion by oils.

- **Facial Afro-Caribbean Childhood Eruption (FACE)** This condition (rediscovered by Hywel Williams) was described by Marten as an unusual papular and acneiform eruption in black-skinned children (Fig 24.14).
- **Endocrine acne** Hypercortisolism, hyperandrogenism and precocious puberty do not respond to therapy. Polycystic ovarian disease should respond; however, XXY and PAPA syndrome does not.
- **PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne)** is a rare, autosomal dominant early-onset disorder due to a mutation in the proline serine threonine phosphatase interacting gene (PSTPIP1). It does respond to anakinra, a recombinant human interleukin receptor antagonist.

Factors that affect acne

- **Medicaments** Topical steroids aggravate acne. Hair greases or pomades may spread onto the forehead (Fig. 24.15) and occlude the pilosebaceous orifices resulting in comedones and acne. There is a condition in black races caused by the application of oil to the limbs, which results in a pustular (Fig. 24.16) and subsequently atrophic eruption, known as *dermatitis cruris pustulosa et atrophicans*.
- **Occlusive circumstances** Acne may be produced by changes in the microenvironment of the skin. Tight-fitting jeans may occlude the pilosebaceous ducts and cause acne on the buttocks and thighs (Fig. 24.17). Prolonged sitting in high-backed chairs, particularly plastic, induces sweating and hydration of the skin and may cause follicular occlusion and acne.

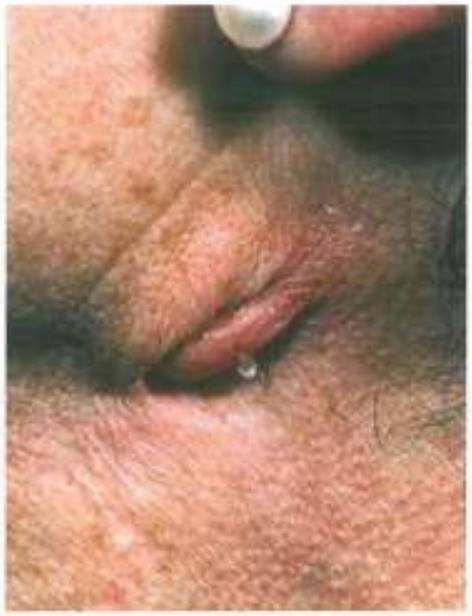


Fig. 24.18 Fiddler's neck. This is due to repeated frictional and mechanical obstruction of the outlet of the pilosebaceous unit.

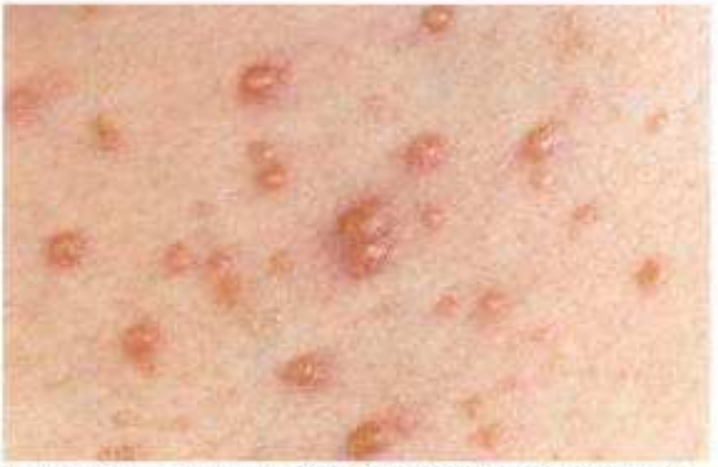


Fig. 24.19 Drug-induced acne. Steroid-induced acne is usually monomorphic. Pustules are predominantly represented here.

- **Acne mechanica** Repeated frictional and mechanical obstruction of the pilosebaceous outlet is thought to be responsible for such conditions as fiddler's neck (Fig. 24.18).
- **Anti-epidermal growth factor monoclonal antibodies** (e.g. cetuximab) cause acne and also hypertrichosis, increased pigmentation, xerosis and paronychia. These drugs are used to treat squamous cell carcinoma of the head, neck and lung. Epidermal growth factor plays a key role in follicular homeostasis, keratinocyte signalling and mediation of the inflammatory response. The acne usually responds to oral minocycline.
- **Ciclosporin** causes sebaceous gland hyperplasia, epidermal cysts, acne, folliculitis, keratosis pilaris and hypertrichosis.
- **Climatic conditions** In predisposed individuals, acne often becomes worse in hot and humid, particularly tropical, climates. This presented a problem for British troops in the Far East during World War II, but not for Americans in Vietnam, probably because those with significant acne were excluded. A variation is *Majorca acne*, a condition in which small follicular papules occur, mainly on the upper trunk, during a holiday in the sun. This may be caused by follicular occlusion secondary to epidermal overhydration, possibly exacerbated by suntan oils.
- **Industrial** *Chloracne* results from exposure to halogenated hydrocarbons. An epidemic in Taiwan in the 1970s was caused by the ingestion of rice that had been cooked in oil contaminated with polychlorinated biphenyls. Transplacental changes occurred in off-spring born to these patients up to 10 years later. These children had acne together with teeth, gum and fingernail abnormalities.
- **TCDD poisoning** Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) was used to poison president Yushchenko in Kiev in 2004. It produces a disfiguring condition of microcomedones and macrocysts. It does not respond to isotretinoin, because it is not a choracne, but a CYP1A1 gene-activated hamartomatous condition. An outbreak occurred after an industrial accident that released 2,3,7,8-tetrachlorodibenzodioxin (TCDD) at Seveso in 1976. This resulted in an acute erythema on exposed skin followed 1–2 months later by a severe acne that lasted for up to 18 months. High levels of dioxin-like products are found in cigarette smoke and may be responsible for 'smoker's' acne.
- **Drugs** Halogens may also produce acne when used therapeutically or diagnostically. For example, iodides in cough mixtures, seaweed, radiological materials and used in the treatment of thyroid disease may be responsible. Bromides, although rarely given nowadays, cause acne. Phenobarbital, troxidone and isoniazid induce acne.

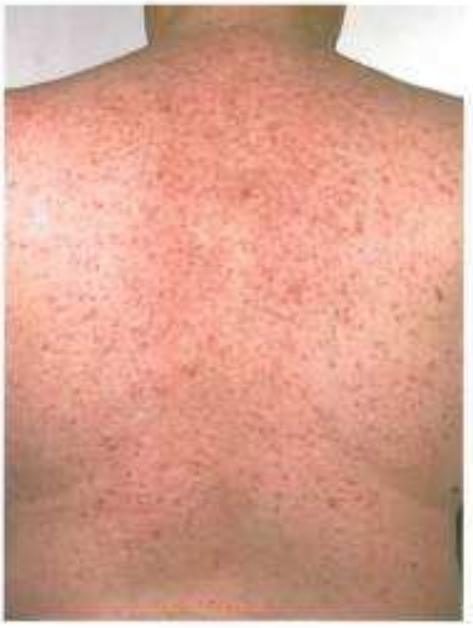


Fig. 24.20 Pityrosporon folliculitis. There is a persistent acneiform eruption with some features of eczema; it responds to broad-spectrum antifungals.

Systemic steroids produce a rather characteristic acne situated on the trunk, shoulders and upper arms, with monomorphic, largely pustular, lesions (Fig. 24.19).

Complications of acne

- **Gram-negative folliculitis** This is a rare condition caused by infection with *Escherichia coli*, *Klebsiella*, *Enterobacteria* or *Proteus* sp. in the anterior nares, the normal ecology of which has been suppressed by long-term antibiotic therapy. There are small superficial pustules with occasionally deep nodules, particularly around the nose. These antibiotics should be stopped and replaced either by ampicillin or cotrimoxazole and, if progressive, by isotretinoin.
- **Pityrosporum folliculitis** Clinically, this is a cross between seborrhoeic eczema and acne (Fig. 24.20); it is thought to be caused by *P. ovale* and responds to broad-spectrum oral antifungal agents (Ch. 15).
- **Acne fulminans** An aggressive ulcerative and crusting acne can occur, particularly in adolescent boys, associated with fever, weight loss, arthralgia, myalgia and erythema nodosum. There may be hepatosplenomegaly and bone pain from aseptic osteolysis. The ESR and white blood count

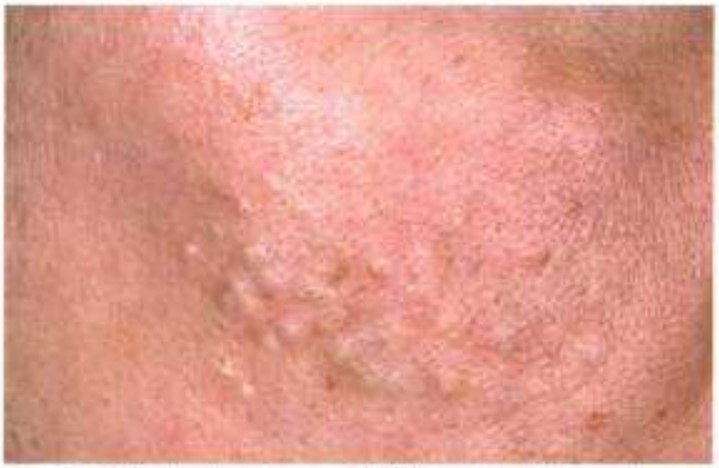


Fig. 24.21 Multiple miliary osteomas. Hard, flesh-coloured, bony papules very occasionally occur in acne in response to inflammation.

may be raised and the liver function tests abnormal. It may represent an abnormal immune reaction to *P. acnes* or be induced by isotretinoin or testosterone. It is treated with prednisolone 0.5–1 mg/kg body weight daily over 6 weeks and then oral isotretinoin (0.5 mg/kg per day) should be instituted.

- **Multiple miliary osteomas** Hard, pea-sized papules occur under the skin (Fig. 24.21) and can be extruded via incision. Topical isotretinoin has been reported as being helpful (0.05%). It is an uncommon response to inflammation. Osteomas may also be found in haematomas and certain cutaneous tumours.

Management

It is important to determine the effect on the patient's morale and the degree of damage to the skin. Mild acne may be acceptable to a teenager if his or her peers are similarly affected, but moderate acne may be more difficult to cope with and can sometimes completely interfere with the patient's life. The indications for energetic systemic therapy are deep papules (which are usually painful), nodules, cysts, scarring and post-inflammatory hyperpigmentation. Postinflammatory hyperpigmentation and scarring must be prevented because the former takes a long time to clear and the latter is permanent.

Topical therapy

Topical therapy is satisfactory for mild adolescent acne vulgaris and mild acne in pregnancy, and as an adjunct to systemic therapy. The face is more responsive than the trunk. Topical preparations are largely antibacterial or keratolytic, reducing the faulty keratinization at the level of the pilosebaceous duct. They are often available in combined formulations, which is justifiable since there is no single answer to the therapy of acne.

- **Benzoyl peroxide** This is an effective antibacterial and comedolytic agent. It is sometimes combined with other antibacterials or sulphur. It may irritate the skin and it is wise to start with the weakest strength, on alternate nights.
- **Retinoic acid** This keratolytic agent increases basal cell mitosis and epithelial turnover, disrupts the comedones and appears to normalize the maturation of follicular epithelium and thus reduce inflammation. Initially, however, it causes inflammation, which some patients find unacceptable. It is recommended for the postinflammatory pigmentation seen so commonly in black skin. The melanin is now thought to be epidermal rather than dermal and retinoids may be useful topically. Retinoids are also available topically combined with erythromycin.
- **Sulphur, salicyclic acid and resorcinol** Resorcinol (1,3-dihydroxybenzene), often used in combination with salicyclic acid and sulphur, is thought to be keratolytic.
- **Topical antibiotics** Benzoyl peroxide and 1% clindamycin are the most commonly used topical antibacterials for acne. Taken orally, clindamycin may cause pseudomembranous colitis and there have been fears that this might also result from absorption of topical preparations, although these anxieties have not been realized. Bacteriologists have been concerned lest the use of the preparation might lead to clindamycin-resistant organisms, but this has not occurred after over a decade of use in the USA. Topical erythromycin and tetracycline are less effective than clindamycin. Neomycin and chloramphenicol have been available in combination preparations that contain sulphur and a weak corticosteroid for some years. However, their use has been criticized for several reasons. It has been suggested that percutaneous absorption could lead to systemic toxicity – aplastic anaemia caused by topical chloramphenicol and ototoxicity by topical neomycin – but there is no evidence for this. Nor is there evidence to prove the theory that topical chloramphenicol has increased bacterial resistance to its systemic use in the treatment of typhoid. Although neomycin and chloramphenicol are both potential sensitizers of the skin, contact dermatitis during their use in the treatment of acne is rare. These combination preparations sometimes contain very weak corticosteroids. Although steroids should not be used on their own for acne, they do reduce the inflammatory effects of keratolytics (which some patients find unacceptable) and are, therefore, permissible.
- **Ultraviolet light** Many patients note that their acne is much improved in the summer. Ultraviolet B has been used therapeutically in doses sufficient to produce mild erythema and consequently desquamation of the skin. It is thought to act by damaging sebaceous glands or killing *P. acne* directly.

Systemic antibiotics

Systemic antibiotics are the mainstay of therapy. Penicillin is ineffective, but tetracyclines, erythromycin, trimethoprim, septrin, flucloxacillin and ampicillin are all effective as they concentrate in the pilosebaceous apparatus. They decrease free fatty acid concentrations in sebum by modifying the action of bacterial lipases, and they also reduce the inflammation of acne by inhibiting neutrophil chemotaxis. Individuals vary in their responsiveness to antibiotics and improvement often takes at least a month.

It is usual to start with a tetracycline, such as oxytetracycline, 250 mg twice daily, which should be taken half an hour before food in order to enhance absorption and must not be taken at the same time as milk products, which reduce absorption. Occasionally, higher doses are required. For those who do not respond, minocycline is an effective alternative. It is a semisynthetic broad-spectrum antibiotic that is more lipid soluble than other tetracyclines, with excellent sebum penetration, and has a longer half-life so may be given once daily. It has a greater antibacterial activity in vivo against staphylococci and propionibacteria than tetracycline. Other alternatives are erythromycin and trimethoprim; the latter probably alone rather than in combination with sulphonamides in view of risk of hypersensitivity reactions. Side-effects are not common but antibiotics should be used with care in renal or hepatic insufficiency and pregnancy, although erythromycin appears safe. Most severe adverse drug reactions are idiosyncratic but benign intracranial hypertension, blue-black pigmentation of the nails, adult teeth, mucous membranes and internal organs may occur with tetracyclines and the bones and teeth of infants may be stained if they are taken during pregnancy. Minocycline occasionally may cause polyarthralgia and hepatitis associated with positive antinuclear antibodies but negative DNA antibodies.

If effective, antibiotics should be given for a minimum of 6 months or longer. Antibiotic-resistant propionibacteria do occasionally occur with tetracyclines. Topical erythromycin (4%) may overcome this.

Hormonal therapy

- **High-dose oestrogen therapy** Oral contraceptives that contain 50 mg ethinylestradiol are of some benefit in women with a pronounced premenstrual flare. Conversely, progesterone-containing oral contraceptives may exacerbate this type of acne and should be avoided.
- **Combined antiandrogen and oestrogen therapy** Cyproterone acetate limits the conversion of testosterone to the highly potent androgen dihydrotestosterone. The combination of 2 mg cyproterone acetate and 35 mg ethinylestradiol (Dianette) reduces sebum production. 2 mg cyproterone acetate is low and it is sometimes necessary to combine Dianette with an extra 50 or 100 mg of cyproterone from days 5 to 15 of the cycle. The side-effects of oral contraceptives are well known. The major side-effect of cyproterone acetate is that it will feminize a male fetus, so it is always combined with an estrogen to prevent conception. Topical cyproterone acetate was thought to be ineffective but it has been reported to be useful in a liposome base.

Systemic retinoid therapy

Acne conglobata in particular was notoriously difficult to treat (radiation was often resorted to in the 1940s–60s; Fig. 24.22) until the advent of 13-*cis*-retinoic acid (isotretinoin: Roaccutane, UK; Accutane, USA), a synthetic derivative of vitamin A. It was a major therapeutic advance (Figs 24.23 and 24.24) in the late 1970s that:

- reduces sebum excretion by 90% within a month; this returns to normal after cessation of therapy without a relapse
- reduces the microorganisms, particularly *P. acnes*, both at the surface and within the pilosebaceous duct to infantile levels
- decreases the plugging of the lining of the duct
- reduces inflammation and chemotaxis
- profoundly influences epithelial proliferation and differentiation such that the sebaceous glands are returned to their prepubertal state.

This drug is the treatment of choice for nodulocystic acne, for acne that is unresponsive to adequate conventional therapy and, particularly, for acne that causes scarring. It is also indicated in patients with psychological distress, antibiotic resistance and Gram-negative folliculitis. It is given orally in daily doses of 1 mg/kg for 4 months (others start at lower doses and gradually increase). Like other systemic treatments for acne, it does not work immediately, but an effect should be seen within 6 weeks. Most patients report it to be the best treatment that they have ever had, particularly as the condition continues to improve after cessation of therapy. The face, however, responds better than the trunk. One course is usually sufficient but up to 20% may require a second course, particularly patients in their early teens and those with acne on the chest and back or with acne that has been present for less than 6 years.

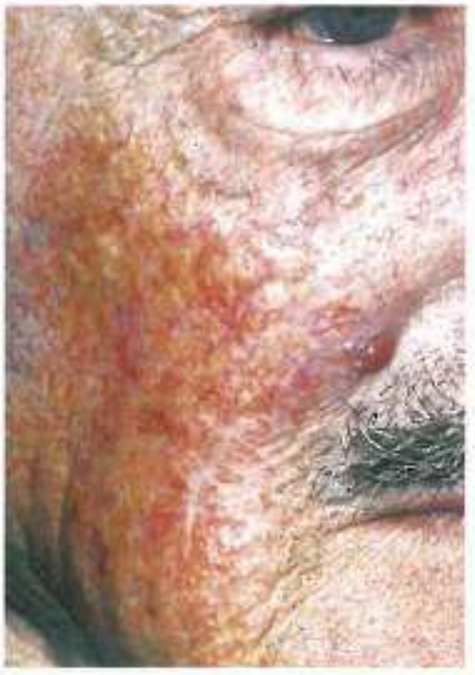


Fig. 24.22 Treatment of acne with X-irradiation. This shows radiodermatitis. Although effective for acne, the long-term effects, including radiodermatitis skin cancer, are unacceptable.

All develop dryness, particularly of the lips (Fig. 24.25), and some get eczema (Fig. 24.26), but not severe enough to warrant the discontinuation of treatment. Nose-bleeds may occur in those who are predisposed. Arthralgias and myalgias occasionally occur, especially in adolescents. Headaches may indicate benign intracranial hypertension, which is a contraindication to its use. Diffuse interstitial hyperostosis is rare. The drug causes temporary hyperlipidaemia and, as it is metabolized through the liver, it is wise to measure both lipid levels and liver function prior to therapy. Depression, hair fall and pyogenic granulomas have also been described but they are rare.

The most important side-effect is teratogenicity. The drug is only prescribable in the UK by dermatologists, and there have been a number of unplanned pregnancies. In the USA, where its prescription is not restricted, there have been more. It is unwise to prescribe the drug without concomitant adequate contraception, or without adequate discussion between

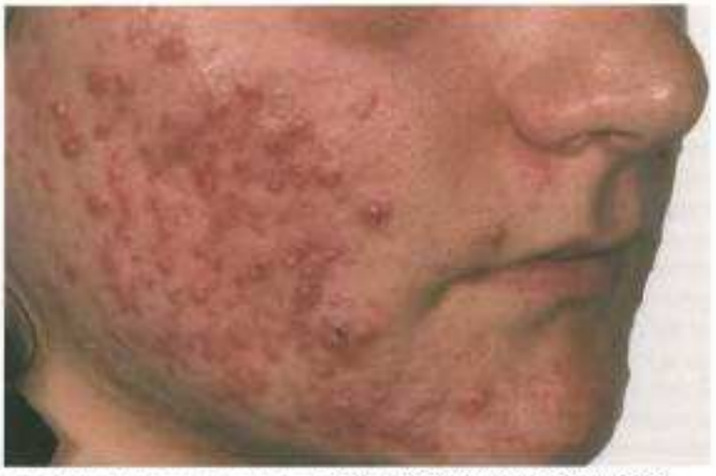


Fig. 24.23 Treatment of acne. Isotretinoin is indicated for nodulocystic acne. It is usually taken for 4 months and induces prolonged remissions but it has side-effects, including teratogenicity.

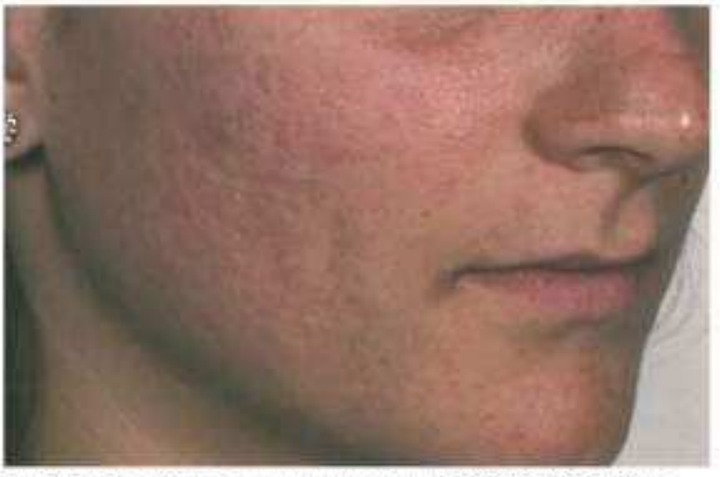


Fig. 24.24 Treatment of acne with isotretinoin. This patient (Fig. 24.23) is shown 16 weeks after starting treatment.

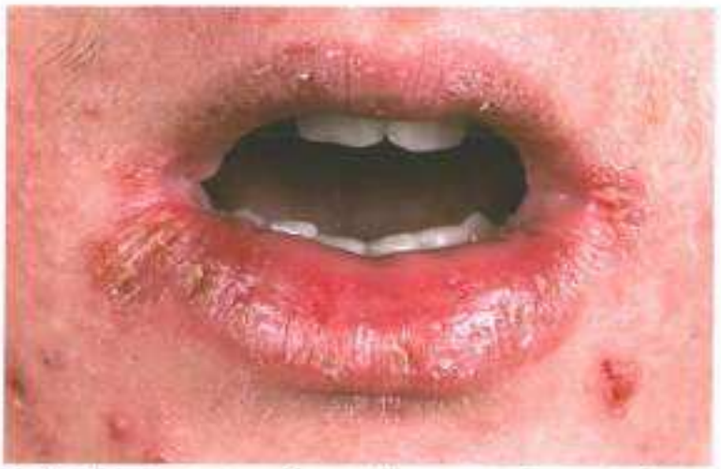


Fig. 24.25 Treatment of acne. Dryness of the mucous membranes is a universal side-effect of isotretinoin, but teratogenicity is the most serious hazard.

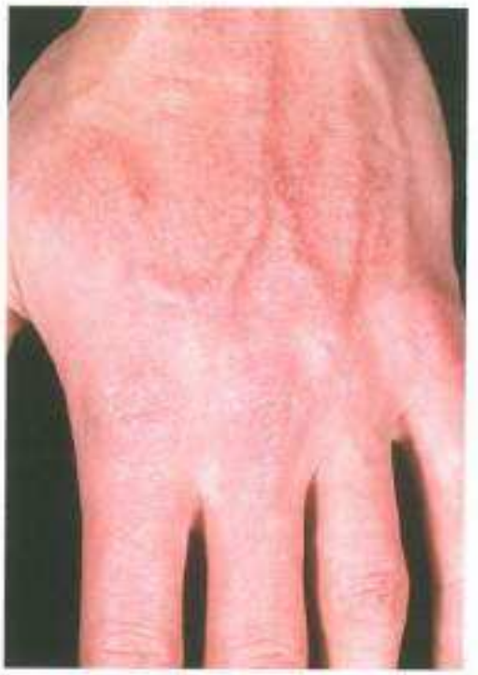


Fig. 24.26 Treatment of acne. Isotretinoin profoundly reduces sebum excretion. Dryness and sometimes eczema results.

the woman, her family practitioner and the dermatologist. Contraception should be continued for at least 3 months after cessation of treatment.

Other therapies

- **Intralesional triamcinolone** Large inflamed cysts (Fig. 24.27) may be injected with small amounts (less than 0.1 ml) of 10 mg/ml triamcinolone, having first evacuated any material within the cyst. Atrophy may result if the steroid is injected too deeply. Incision is inappropriate.
- **Surgery** Unsightly scars and persistent cysts, when no longer inflamed, may be excised. Dermabrasion and collagen implants have met with variable results.
- **Photodynamic therapy** This may induce temporary remission, but can cause discomfort (burning sensation) and hyperpigmentation in dark skins.

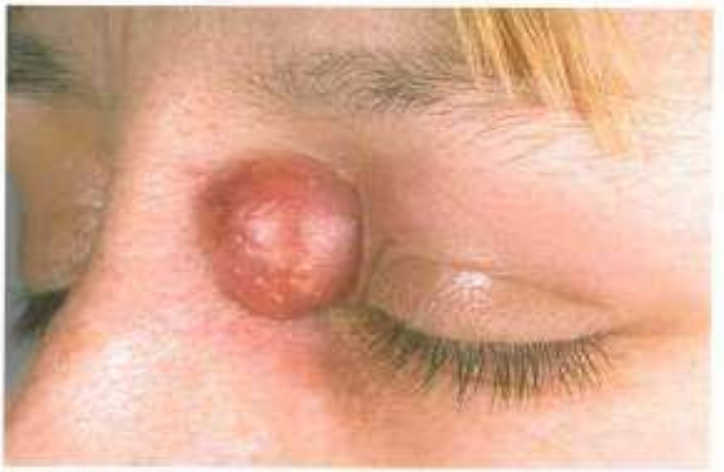


Fig. 24.27 Acne cyst. Large inflamed cysts may be seen in acne conglobata, and sometimes occur with minimal acne elsewhere. The lesions can be drained and then injected with triamcinolone.

ACNE EXCORIÉE DES JEUNES FILLES

A facial disorder secondary to an obsessional and neurotic tendency to interfere with the skin.

Aetiology

The name is a misnomer for, although it is almost exclusively confined to women, they are not particularly 'jeunes' and have very little if any preceding acne. Although many patients with acne pick at and squeeze their spots to a limited extent, women with this disorder do so in an obsessional and destructive manner.

Clinical Features

Symptoms

Rash on the face (Fig. 24.28).

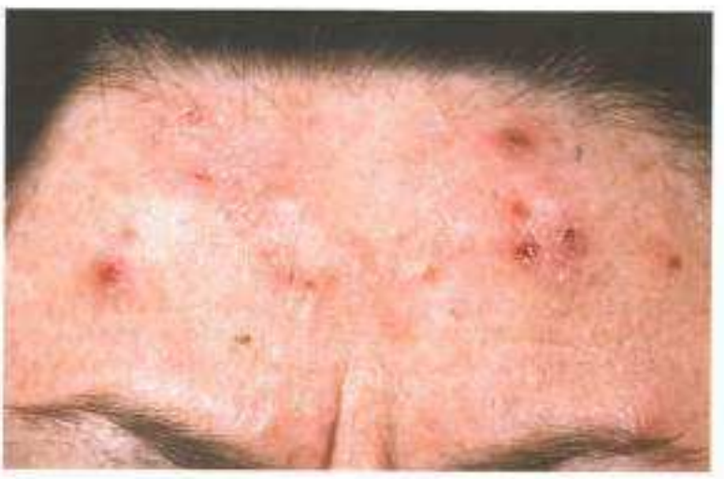


Fig. 24.28 Acne excoriée des jeunes filles. This is a chronic neurotic disorder of adult women who admit that they pick and squeeze at their facial skin. Unsightly excoriations result.

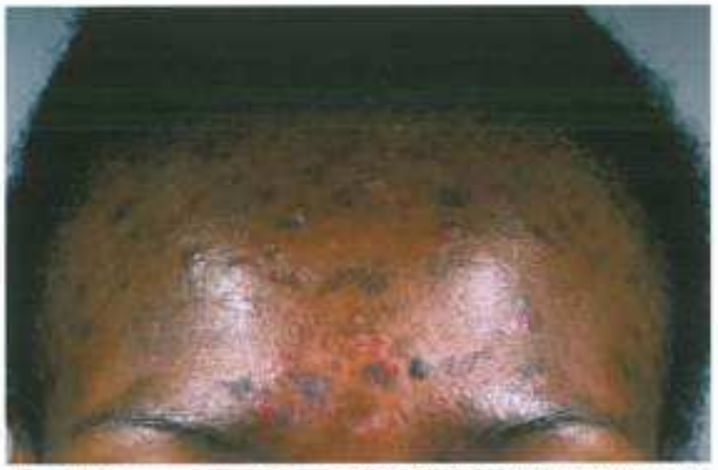


Fig. 24.29 Acne excoriée des jeunes filles. There is rarely any acne to see and the patients are not particularly young. Excoriations are present with post inflammatory hyperpigmentation. It is difficult to treat.

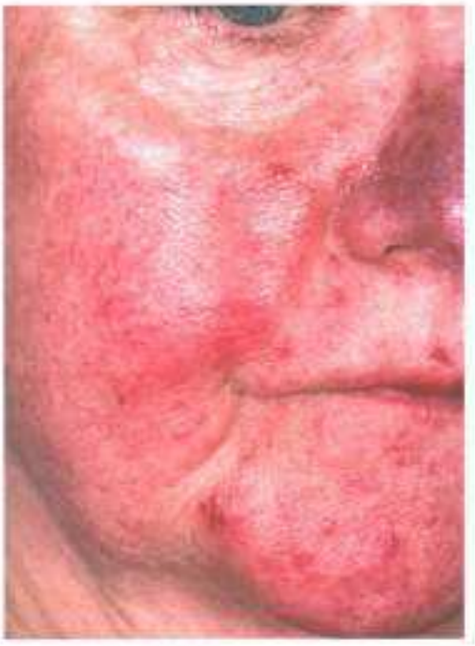


Fig. 24.30 Rosacea. There is a background redness to the skin and a tendancy to flush. Papules and pustules are present but not comedones, which distinguishes it from acne. It had deteriorated because she was applying hydrocortisone.

Morphology

The physical signs are almost exclusively secondary to interference with the skin, and unsightly excoriations, postinflammatory hyperpigmentation and scarring (Fig. 24.29) result.

Distribution

The forehead, cheeks, chin and jaw are primarily affected.

Management

Although these women freely admit that they pick at their skin, it is difficult to break the habit. It may represent a form of defence, resulting from an inadequate or unhappy life. Psychiatric assistance does not particularly benefit the skin condition.

Rosacea

A cutaneous vascular facial disorder characterized by papules and pustules often associated with erythema and flushing.

Aetiology

The disorder is common in fair-skinned individuals and occurs equally in both sexes from the fourth decade onwards. It does occur in Asians but not in type VI skins. In some, the disorder lasts a few months and then goes into remission, although often not permanently. Others have the disease chronically to some degree or another. Histologically, there is vascular dilatation, sebaceous gland hyperplasia and marked solar elastosis. The cause is probably solar damage in a fair skin leading to vasomotor instability, which is apparent clinically from the erythema of the face and a tendency to flush readily. This in turn may be influenced by:

- **Diet** There have been many claims for a gastrointestinal disturbance in rosacea, including *Helicobacter pylori* infection, but none has been substantiated. However, rosacea is aggravated by hot drinks, alcohol and spicy foods because they are vasodilators.
- **Climate** Fluctuations in temperature aggravate the disorder. Patients note that they tend to flush when they move from a warm environment out into the cold and vice-versa. Similarly, warm climates aggravate rosacea. It has been proposed that the vasomotor tone of the facial blood vessels is impaired.
- **Topical glucocorticosteroids** These agents aggravate rosacea (Fig. 24.30). The erroneous practice of prescribing topical steroids to treat rosacea is uncommon nowadays, but side-effects may result where steroids can be bought over the counter. Moreover, patients may be given them by well-meaning friends or use a steroid prescribed for another condition. Topical steroids are vasoconstrictors so they may appear to be a logical treatment for a disease where vasodilatation is a prominent feature. Indeed the rosacea is often temporarily improved but deteriorates a short while after cessation of therapy, probably because of a subsequent vasodilation. As a result, every time the patient stops using the steroid the condition flares and in the mistaken belief that the steroid is helping to control an otherwise deteriorating condition, the patient reapplies it to calm it. A vicious circle of pseudoaddiction results.

Fig. 24.31 Demodecosis. The *demodex* mite is a normal inhabitant of the pilosebaceous apparatus. Their numbers are increased in rosacea, but considerably so in the immunosuppressed, including haematological malignancies, causing widespread facial papules and pustules.

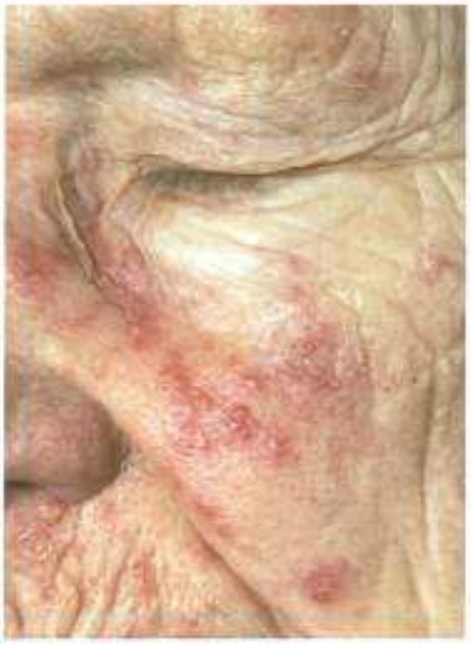


Fig. 24.32 Rosacea. There are papules, pustules and erythema on the cheeks. Note the solar elastosis and furrowing of the skin. Skin damage is an important cause of rosacea.

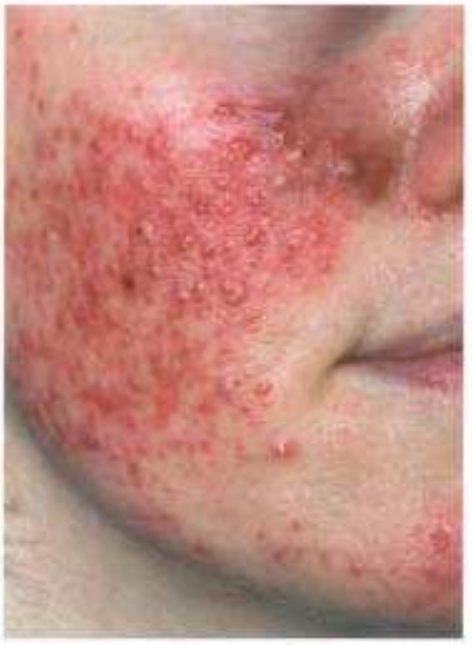


Fig. 24.33 Rosacea. There is a background redness to the skin and a tendency to flush. Papules and pustules are present but not comedones, which distinguishes it from acne.

- ***Demodex folliculorum* and *D. brevis*** These mites are normal inhabitants of the follicular apparatus, found deep in the sebaceous and meibomian glands. They feed on the contents of the cells, especially sebum. They may be increased in number in rosacea (although their relevance is obscure and their numbers do not decline with treatment) and considerably so (*demodecosis*) in the immunosuppressed, including those with haematological malignancies (Fig. 24.31) and HIV disease and those using topical steroids and tacrolimus. Biopsy shows *demodex* mites in the follicular infundibulum and a dense perivascular and perifollicular lymphohistiocytic infiltrate and abundant neutrophils and occasional multinucleated histiocytes. It may respond to systemic metronidazole and topical crotamiton, γ-benzene hexachloride or metronidazole.

Clinical Features

Symptoms

The patient complains of spots, often with yellow heads, on the face and notes a tendency to flush easily and to go 'as red as a beetroot'.

Morphology

Red papules (Figs 24.32 and 24.33), yellow pustules (Fig. 24.34) and a diffuse erythema and telangiectasia of the face.

Distribution

The cheeks, nose, forehead and chin are affected.

Variants of rosacea

- **Rhinophyma** The nose and chin may be afflicted by an exuberant overgrowth of soft tissues, secondary to sebaceous gland hypertrophy. This condition, which is more common in males, may occur with little concomitant rosacea.
- **Erythematotelangiectatic rosacea** Occasionally only the nose is affected by erythema (Fig. 24.35) with little elsewhere.
- **Ocular complications** The eyes may be affected. The patient complains of discomfort or grittiness in the eyes. Conjunctivitis, blepharitis and keratitis, with ulceration and vascularization of the cornea, may be present.

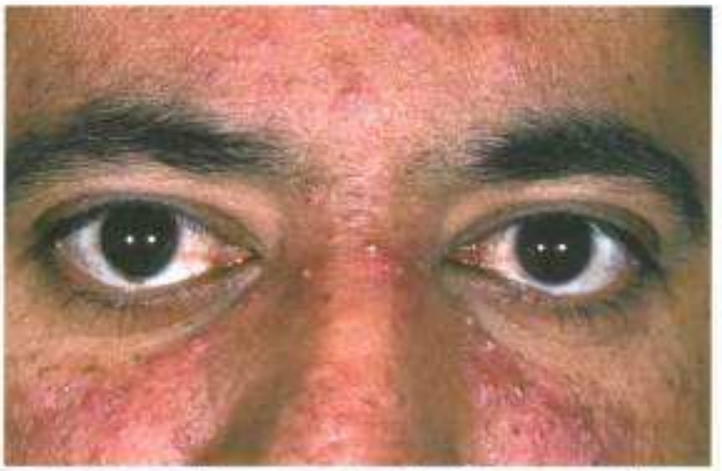


Fig. 24.34 Rosacea. Rosacea is a disorder of fair skin but may occur in Asian but not in black skin. Papules and pustules are easily visible.

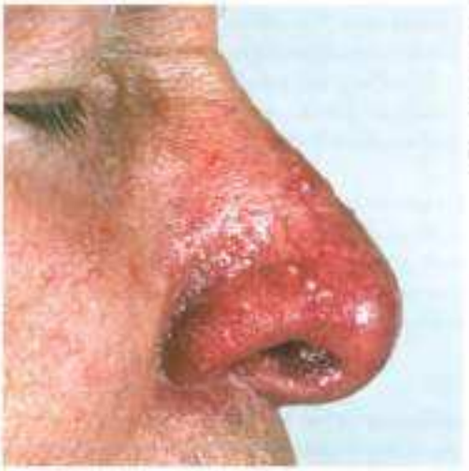


Fig. 24.35 Rosacea. Occasionally the nose may be red without involvement elsewhere. The pustules respond well to antibiotic therapy, but the erythema remains.

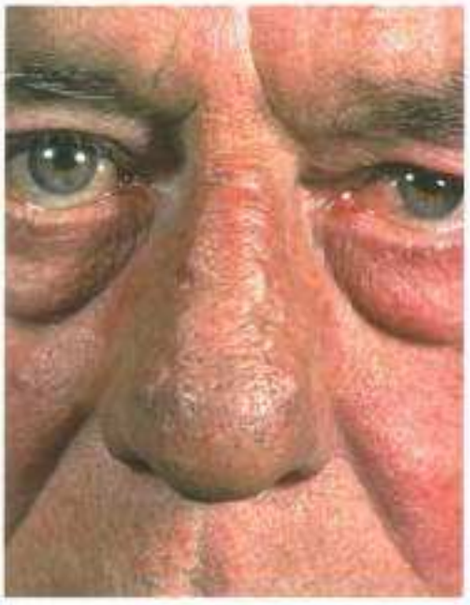


Fig. 24.36 Lymphoedema and rhinophyma. Lymphoedema of the eyelids may occur in addition to rhinophyma or rosacea.

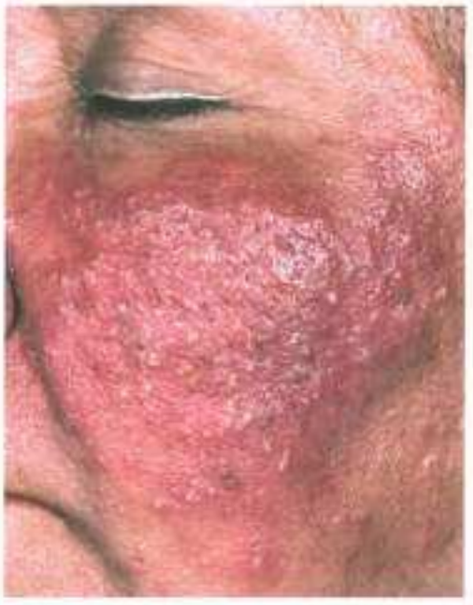


Fig. 24.37 Pyoderma faciale. There is a large oedematous red plaque, mainly on the cheeks made up of papules and pustules. It erupts suddenly. Swabs are negative microbiologically. Superpotent steroids may produce a similar condition.

- **Lymphoedema** around the eyes may be prominent (Fig. 24.36).
- **Pyoderma faciale** (rosacea fulminans) is a rare, sudden, fulminating pyoderma that occurs in females in their early twenties who flush and blush easily. There are papules, pustules, nodules and fluctuant and draining sinuses, producing a purulent, haemorrhagic or oily material in a centrofacial distribution (Fig. 24.37). It was previously known as an explosive postadolescent facial acne of females, but the vasomotor instability indicates that it is a form of rosacea. It should be treated with isotretinoin (and some suggest systemic steroids temporarily in addition).

Differential Diagnosis

Rosacea is sometimes confused with acne and has in the past been called 'acne rosacea', but there is no aetiological resemblance to acne and the term should be dropped. Acne occurs in the second and third decades whereas rosacea occurs later. The skin is greasy in acne but not in rosacea where there is a tendency to flush. Comedone, cysts and scars do not occur in rosacea and the response to antibiotics is much more rapid. Occasionally, as might be expected with two common conditions, patients may have acne followed by rosacea.

Patients who work with visual display units often complain of itching and burning on the face and this has sometimes been confused with acne or rosacea. However, there are usually few visible physical signs and, although the symptoms are more common amongst highly exposed individuals, the objective signs are no more than are seen in controls. Whether this is a psychological condition or a real one is, therefore, not yet proven.

Other causes of flushing (blushing, menopause, vasodilators such as cyclophosphamide, metronidazole, alcohol and antabuse, food intolerance, carcinoid syndrome and mastocytosis) may be excluded on the basis of the history.

Occasionally too, patients complain bitterly of burning of the face and yet there are no abnormal physical signs. They too are often labelled as having rosacea but are usually suffering from *dysmorphophobia*, a psychological condition that is extremely difficult to rectify although long-term very low doses of oral isotretinoin can sometimes be helpful.

Management

Rosacea is a gratifying disorder to treat but relapse is common.

- **Antibiotics** Tetracyclines, erythromycin, septrin or metronidazole are all effective, usually in small doses, for example oxytetracycline 250 mg twice daily. Rosacea responds within days (much more quickly than acne). The drugs have to be taken long-term to maintain control, but lower doses are required than for acne, and patients can tailor the dose to give exact control. For example, oxytetracycline 250 mg on alternate days may be quite sufficient.
- **Topical remedies** No topical remedy is very effective and rosacea is best managed systemically. However 1% metronidazole may be of benefit. Equally, sulphur cream starting at 1% and gradually increasing thereafter is a time-honoured preparation. Both are useful in pregnancy when tetracyclines, in particular, are contraindicated; erythromycin is acceptable after the first trimester if the rosacea is severe. Azelaic acid (a naturally occurring saturated dicarboxylic acid) possesses antibacterial, comedolytic, anti-inflammatory and antimelanocytic properties and is sometimes helpful.
- **Diet** Hot drinks such as tea or coffee exacerbate rosacea. Curries and other spicy cuisine should also be restricted. It is important that alcohol misuse is diagnosed and managed appropriately.
- **Topical steroid abuse** It is essential to discover whether patients are applying topical steroids. If so, the patient should stop the drug and be warned that there will be a rebound for 3–4 days before the antibiotics begin to take effect.
- **Low-dose isotretinoin** May be effective if other measures fail.

Management of variants of rosacea

- **Red nose** Some patients have erythema of the nose only, with little in the way of papules and pustules. This disorder does not respond well to any treatment, but sunlight, alcohol (Fig. 24.38) and other vasodilators must be avoided.
- **Rhinophyma** The hypertrophic sebaceous glands can be pared away and the nose remodelled by a plastic surgeon (Figs 24.39 and 24.40). Rhinophyma does not respond to antibiotics.
- **Telangiectasia** The background erythema and telangiectasia of rosacea (Fig. 24.41) is more diffuse than that of essential telangiectasia (Fig. 24.42). It may occur on its own without papules or pustules. Both conditions may be helped by lasers.
- **Eye complications** Antibiotics are of benefit, but the ocular changes are complicated and referral to an ophthalmologist is recommended.
- **Lymphoedema** This does not respond to antibiotics but the excess skin may be removed by a plastic surgeon.

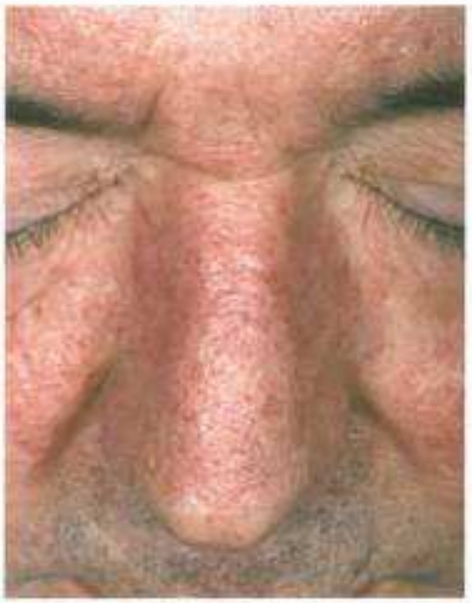


Fig. 24.38 Alcohol misuse. Alcohol is a vasodilator and ultimately causes a subtle telangiectasia, especially of the face. Alcohol exacerbates various skin disorders, including rosacea.

Perioral and periorbital dermatitis

A papulopustular eruption around the mouth or eyes secondary to the misuse of topical glucocorticosteroids.

Aetiology

Essentially, the condition is acneiform and the term 'dermatitis' is singularly unhelpful and misleading. Although it probably existed before the advent of topical steroids, it is now almost invariably associated with inappropriate treatment with topical steroids, mistakenly prescribed by a doctor, obtained from a well-meaning friend or prescribed for an unrelated condition. Some have proposed that overhydration of the skin by moisturizers leads to irritation and impairment of skin barrier function and proliferation of skin flora. The initial disorder is either a mild seborrhoeic eczema or a mild acne around the nose, mouth or eye. Hydrocortisone is the treatment of choice for seborrhoeic eczema but perioral and periorbital dermatitis may result if a more potent steroid is used. If the initial condition is acne, even hydrocortisone will cause the disorder. (Acne is often misdiagnosed as eczema when it is itchy.) The steroid seems to work at first, but each time the treatment is discontinued the condi-

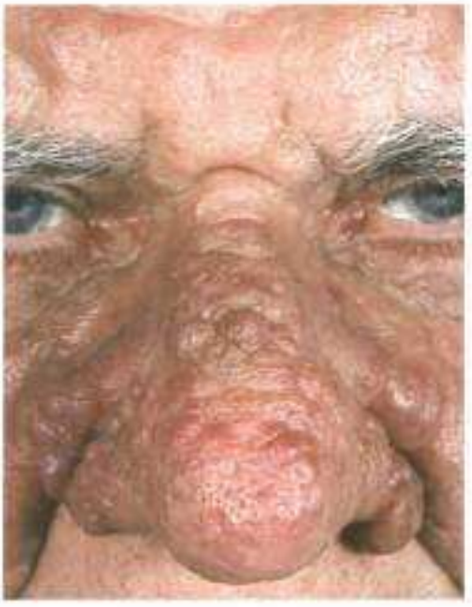


Fig. 24.39 Rhinophyma treated surgically. The hypertrophic sebaceous glands can be pared away effectively and the appearance remodelled.

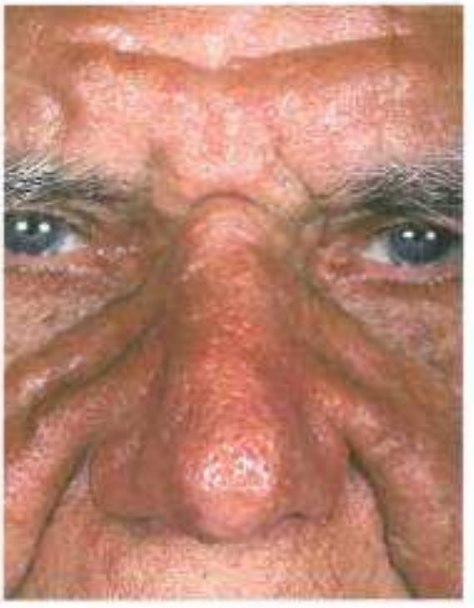


Fig. 24.40 Rhinophyma treated surgically. The patient (Fig. 24.39) is shown 2 months after surgery.

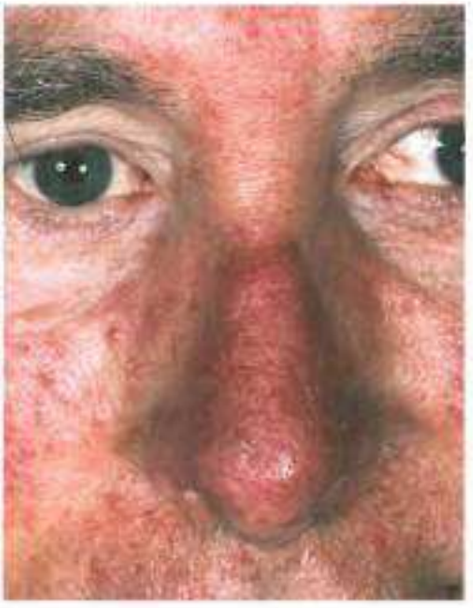


Fig. 24.41 Rosacea. The telangiectasia is prominent on the nose, giving the impression of a diffuse erythema. There are papules on the cheeks, which aid the diagnosis. Telangiectasia may sometimes be the sole manifestation. Lasers may be of benefit.

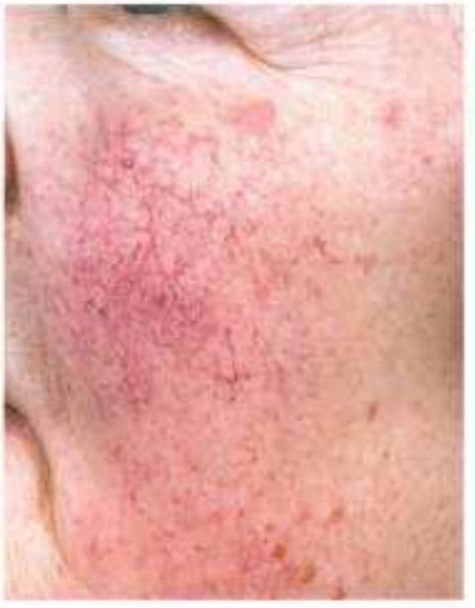


Fig. 24.42 Essential telangiectasia. Probably in part familial, and in part secondary to ultraviolet light, it is treatable with lasers as may be the telangiectasia of rosacea.

tion flares. Re-application of the steroid calms the rash and so many patients are led into believing that the steroid is controlling a progressive disease. Topical steroids are potent acne-inducing agents, and potent steroids should never be prescribed for acne and rarely for eczema of the face. There is also mounting evidence that topical tacrolimus may produce the condition.

Clinical Features

Symptoms

A history of the use of a steroid with deterioration on ceasing to use it.

Morphology

Red papules and pustules, often on a background of erythema and scaling which may simulate eczema. There are no comedones.

Distribution

The condition involves the area of application of the drug, which is usually around the nose and mouth (Fig. 24.43) or around the eye (Figs 24.44 and 24.45) but may be more extensive (Fig. 24.46).

Management

Discontinuation of the steroid and treatment with an antibiotic, for example minocycline MR 100 mg daily for 6 weeks, is successful. After an initial relapse (if the patient has been using the steroid up to the minute of the consultation), the condition begins to improve after 4 days and is very much better at 2 weeks.

Acne agminata

An uncommon eruption on the face of persistent monomorphic brown papules with a granulomatous histology of unknown aetiology.

Aetiology

The histology shows a granulomatous reaction, often with central caseation. The condition was formerly thought to be a tuberculide (hence *lupus miliaris disseminatus faciei*) but it does not respond to antituberculous therapy and any relationship is now discounted.

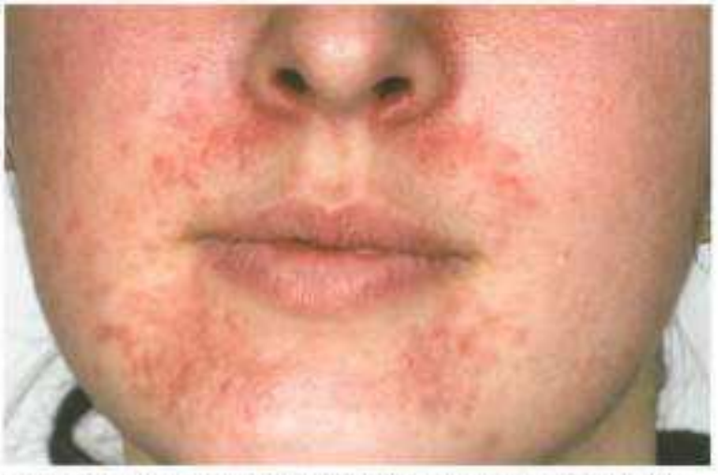


Fig. 24.43 Perioral dermatitis. The distribution around the nose and mouth is typical. Patients observe that the condition flares on stopping the steroid, so they continue to apply it.

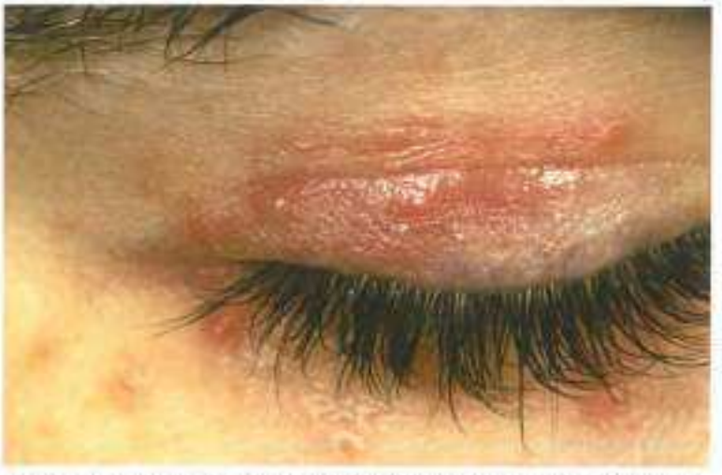


Fig. 24.44 Periorbital dermatitis. There are papules and pustules and the true diagnosis is acne but because they are itchy, patients are often prescribed topical steroids which ultimately make the condition worse.

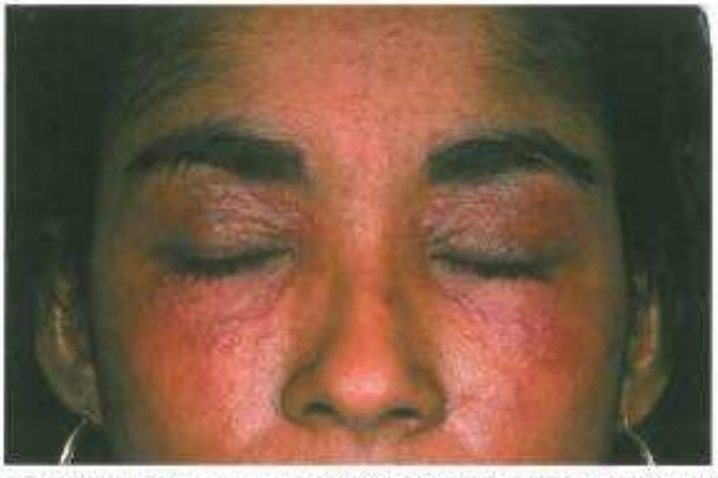


Fig. 24.45 Periorbital dermatitis. There are many small papules. The lesions are acneiform not dermatitic. The patient has been using a superpotent topical steroid.

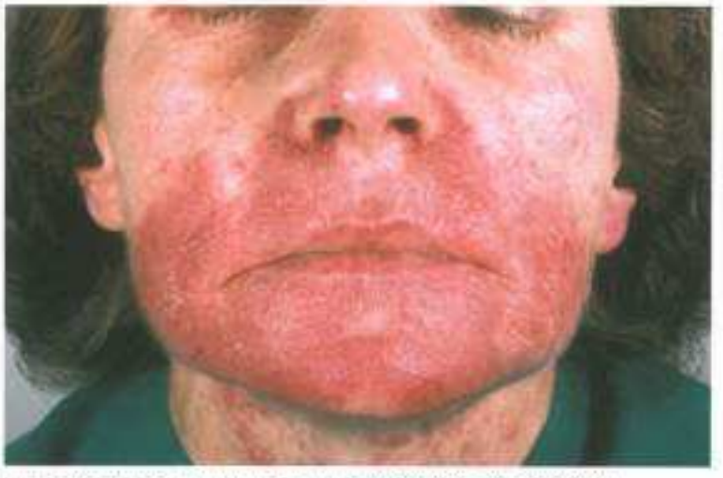


Fig. 24.46 Topical steroid misuse. The overall appearance is of a red eczematous rash around the mouth, but it is composed of papules and pustules, (also to be seen on the neck). She had been mistakenly applying a potent steroid.

Clinical Features

Symptoms

A rash on the face.

Morphology

Monomorphic persistent small brown papules (Fig. 24.47) that ultimately heal and occasionally leave scarring.

Distribution

Symmetrically on the forehead, temples, cheeks, chin and, in particular, on the eyelids – an unusual site for acne vulgaris. It has rarely been described in the axillae.

Management

The condition usually lasts a couple of years. Results of treatment are variable, but systemic antibiotics, isotretinoin and 1450-nm diode lasers are worth trying.

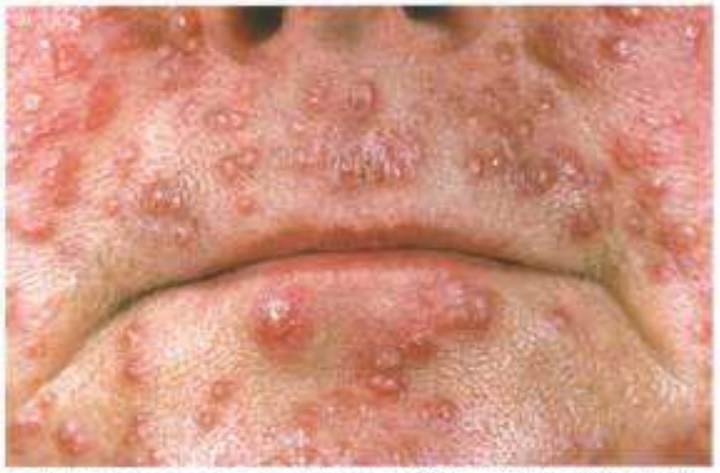


Fig. 24.47 Acne agminata. Monomorphic, persistent, small, red-brown papules occur on the face. The cause of the granulomas is unknown.

Hidradenitis suppurativa

A suppurative inflammation of terminal hair follicles resulting in follicular occlusion with secondary involvement of the associated apocrine, eccrine and sebaceous glands; it affects the axillae and anogenital regions.

Aetiology

The cause is unknown. There is often concomitant acne conglobata and dissecting folliculitis of the scalp, and this association is known as the *follicular occlusion triad*. Sometimes pilonidal sinuses are present, which makes a tetrad of the condition. The disorder has been thought to be one of apocrine glands but some believe it to be a disorder of hair follicular occlusion rather than a primary 'apocrinitis'. It is more common in young females, smokers and the obese. It is possibly more commonly associated with inflammatory bowel disease. If bacteria are cultured from the lesions they are usually commensals and the condition may be an inappropriate response to these flora.

Clinical Features

Symptoms

Uncomfortable, unpleasant destructive sores in the flexures.

Morphology

Indolent pustules and nodules (Fig. 24.48) occur that break down to form abscesses and sinuses, which, in turn, connect. Puckered scarring results.

Distribution

The axillae (Fig. 24.49) and groin.

Management

There is no specific treatment, but loss of weight is mandatory and long-term antibiotics, intralesional steroids, isotretinoin and ciclosporin may be tried. Anti TNF-α drugs (especially infliximab) are proving to be promising in inducing remission. Excision of local areas of affected skin and grafting can be successful if the disease is limited.

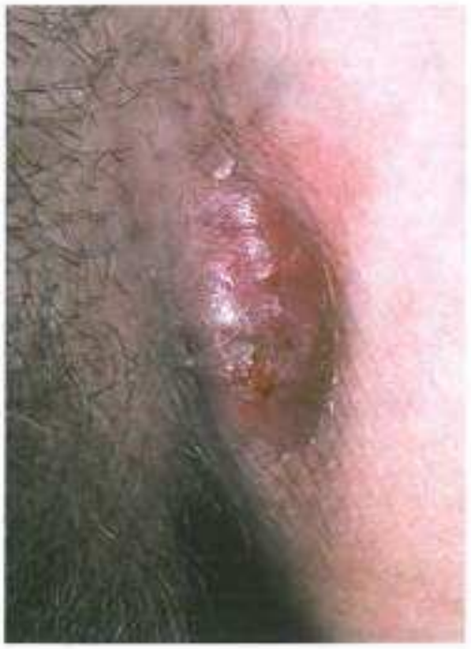


Fig. 24.48 Hidradenitis suppurativa. Large nodules may result, which are painful. Treatment is unsatisfactory. Antibiotics and isotretinoin may be tried. Local excision is helpful but excision and grafting of the area may be necessary.

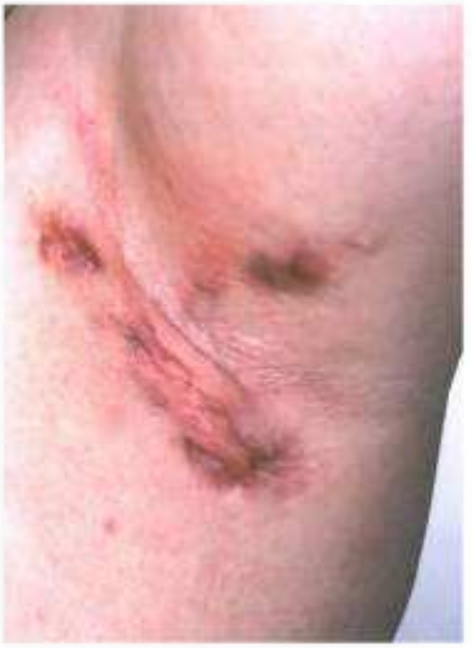


Fig. 24.49 Hidradenitis suppurativa. Sinuses and puckered scarring result from indolent, inflamed papules and nodules in the flexures.

Disorders of the sweat gland

MILIARIA

Miliaria result from sweat gland obstruction following excess sweating.

Aetiology

The three kinds of miliaria which occur depend on the level of obstruction.

Miliaria crystallina is the most superficial, and a vesicle forms just below the stratum corneum. It results from profuse sweating associated with a fever or tropical heat and humidity. It occurs in neonates, probably as a result of a delay in the opening of the sweat duct after birth.

Miliaria rubra (prickly heat) occurs within the stratum malpighii and usually affects individuals within the first few months of arrival in a hot, humid climate. Occlusive clothing and friction aggravate the problem. An identical clinical situation occurs on occlusion with polythene. There is blockage of the intraepidermal part of the sweat duct and a vesicle forms around it.

Miliaria profunda (mammillaria) results from rupture of the sweat duct at the level of the dermo-epidermal junction. It occurs after repeated attacks of miliaria rubra have caused more severe damage to the duct.

Clinical Features

Miliaria crystallina

Symptoms

Asymptomatic.

Morphology

Small (1–2 mm), thin-walled, clear vesicles (Fig. 24.50), like drops of water with no surrounding inflammation, occur in crops. They are very fragile and rupture spontaneously, resulting in a superficial bran-like desquamation.

Distribution

Largely on the trunk.

Miliaria rubra

Symptoms

There are paroxysms of intense pruritus resulting in considerable scratching.

Morphology

Uniform, erythematous non-follicular macules or papules occur in large numbers (Fig. 24.51); these may contain a minute central vesicle or occasionally pustule, which if widespread is sometimes known as *miliaria pustulosa*.

Distribution

In adults, the lesions occur in the flexures and areas of friction from clothing (trunk and neck) but not on the face or volar areas. It can occur in infants in the second week of life, affecting the flexures and, unlike in adults, the face and scalp. It is not uncommon.

Miliaria profunda

Symptoms

Asymptomatic.

Morphology

A large number of small pale or flesh-coloured firm papules.

Distribution

Particularly on the body but also on the limbs.

Fig. 24.50 Miliaria crystallina. Minute, discrete vesicles resulted from profuse sweating secondary to a high fever.

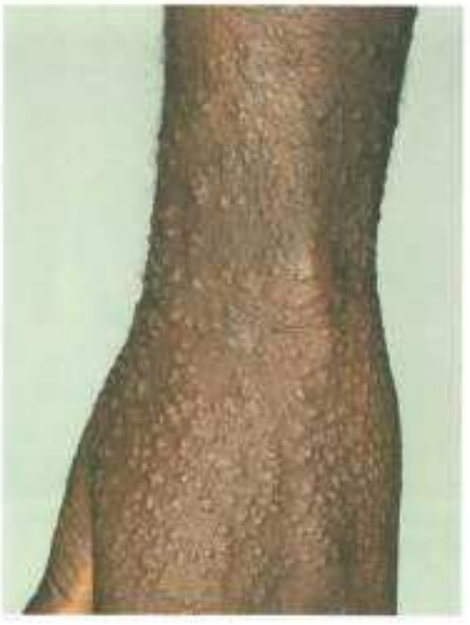


Fig. 24.51 Miliaria rubra. Prickly heat occurs in hot humid conditions and results from blockage of the intraepidermal part of the sweat duct.

Systemic features

Malaise, dyspnoea and tachypnoea with hyperpyrexia and heat exhaustion may occur.

Management

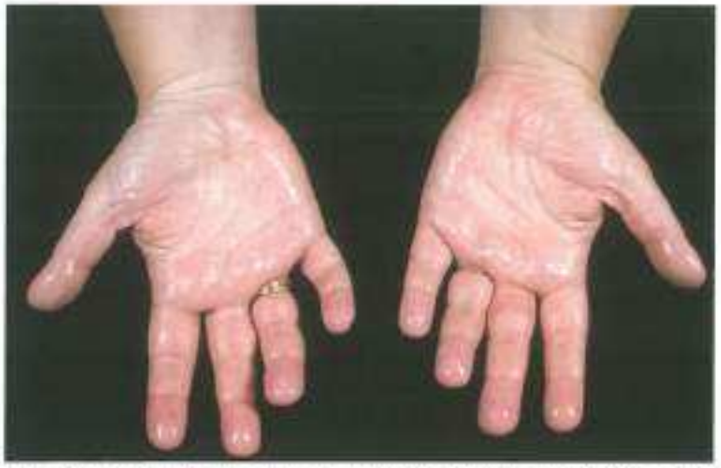
These conditions respond quickly to cooling (a few hours in air conditioning), although this may not always be possible in tropical conditions. Occlusive clothing should be removed. Vitamin C has been said to be helpful. Secondary infection should be treated with systemic antibiotics. Miliaria crystallina subsides without treatment within a few days of cessation of the fever.

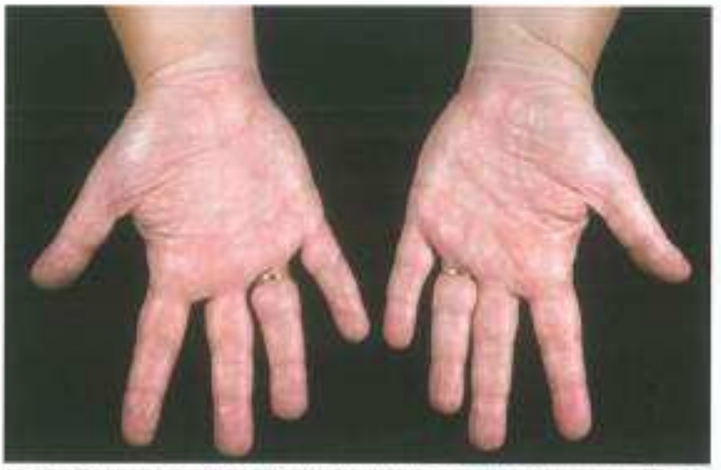
IDIOPATHIC LOCAL HYPERHIDROSIS

An overproduction of sweat from the axillae, palms or soles.

Aetiology

There are two distinct types of eccrine sweat glands, which respond either to heat or to emotion. Those responsible for heat adaptation and thermoregulation are distributed all over the body, except for the palms and soles. The sweat glands in the axillae are under the control of both heat and





Figs 24.52 and 24.53 Hyperhidrosis. Hyperhidrosis may be treated with sympathectomy via a laparoscope. It is an effective treatment but compensatory hyperhidrosis on the body and Horner's syndrome are complications.

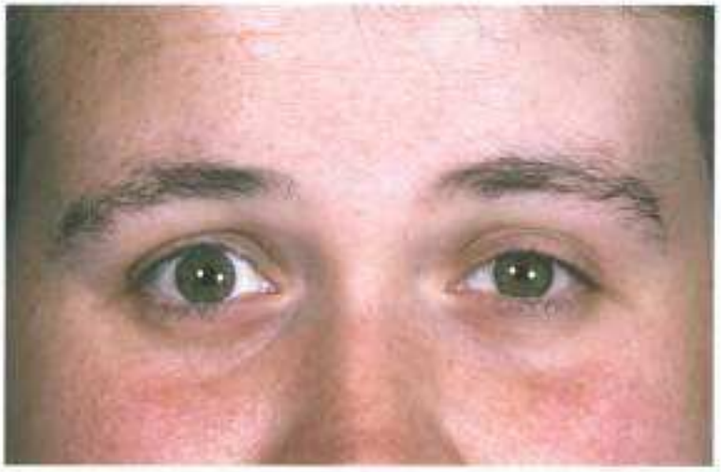


Fig. 24.54 Horner's syndrome. This is the same patient as in Figures 24.52 and 24.53. She developed Horner's syndrome temporarily postoperatively.

emotion. Sweat glands are the only cutaneous appendage on the palms and soles and are most densely distributed there. They are solely under the control of the emotions and localized hyperhidrosis is probably an abnormal response to emotional stimuli in the hypothalamic sweat centres. Idiopathic hyperhidrosis may be limited to the axillae or to the extremities but occasionally both areas are affected. The condition becomes pathological, rather than a normal physiological response, when it interferes with function. It occurs most commonly in adolescents and young adults. It tends to improve as subjects grow older.

Asymmetrical hyperhidrosis may occur following any neurological lesion involving the sympathetic pathway from the brain to the nerve endings. Paroxysmal unilateral hyperhidrosis may result from an intrathoracic neoplasm. Compensatory hyperhidrosis occurs when sweat glands elsewhere are non-functioning and following sympathectomy. Gustatory hyperhidrosis is a very common physiological event affecting the face. Pathologically it may occur in diabetics secondary to autonomic neuropathy or following damage to the sympathetic nerves, particularly around the head and neck. The commonest is within the distribution of the auriculo-temporal nerve following an abscess or surgery in the parotid region (von Frey's syndrome).

Generalized hyperhidrosis occurs in many disorders (thyrotoxicosis, acromegaly, diabetes mellitus and congestive cardiac failure) as a secondary rather than a presenting feature. In phaeochromocytoma it may be the primary complaint. Nocturnal sweating occurs in lymphoma.

There is a rare localized hyperhidrosis of the nose beginning in early childhood that ultimately leads to a diffuse erythema known as *gramulosa rubra nasi*. Fine red papules and beads of sweat may also be seen. The cause is unknown but it sometimes resolves at puberty.

By contrast, *Ross syndrome* is a disorder of reduced sweating (hypohidrosis), leading to compensatory hyperhidrosis associated with tonic (Holmes-Adie) pupils and global areflexia.

Clinical Features

In pathological hyperhidrosis of the palms and soles, the excess sweating is perfectly obvious and the sweat may be seen quite literally dripping onto the floor. Those who suffer from axillary hyperhidrosis will show how the underarm portion of their blouses or shirts is stained and ruined within a few hours of use.

Management

- **Aluminium hexahydrate** Aluminium chloride hexahydrate 20% in absolute anhydrous ethanol may alleviate axillary hyperhidrosis, but disappointing for palmar or plantar disease.
- **Iontophoresis** This is the introduction of an ionized substance through the skin by a direct current. It is useful for palmar/plantar hyperhidrosis. Initially, various substances such as atropine, formaldehyde and anticholinergic drugs (e.g. glycopyrrolate) were introduced by this technique, but tap water alone is effective. Why the sweat glands shut down is unknown. It has been suggested that the sweat glands become blocked or that there is some electrical gradient that controls the movement of sweat along the sweat duct, which is interfered with by iontophoresis. The method involves immersing one hand into a bowl of water with an electrode connected to a galvanic generator delivering direct current. A foot is placed in another bowl of water with an electrode to complete the circuit. The sweating ceases for many weeks and the treatment can be repeated. This treatment is usually carried out under hospital supervision, but there are units available for home use.
- **Surgical sympathectomy** As techniques for sympathectomy improve, this has become a much more effective and safe operation for hyperhidrosis of the palms. It is indicated only for those with severe disease as there can be the disabling side-effect of permanent dryness, scaliness and fissuring of the palms, secondary to the total switching off of the sweat glands. Compensatory hyperhidrosis on the body may occasionally result. The operation may now be performed via a laparoscope inserted into the axilla (Figs 24.52 and 24.53). Horner's syndrome is a complication (Fig. 24.54).

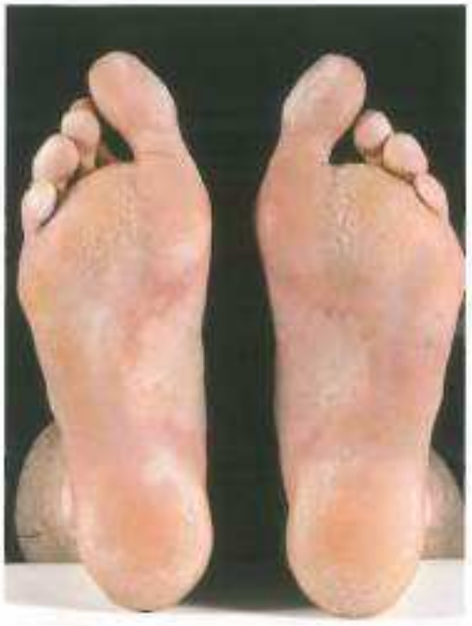


Fig. 24.55 Pitted keratolysis. Organisms, often corynebacteria, invade the damp stratum corneum and superficial erosions result. The instep is usually spared. It is associated with hyperhidrosis. It may respond to antibiotics.

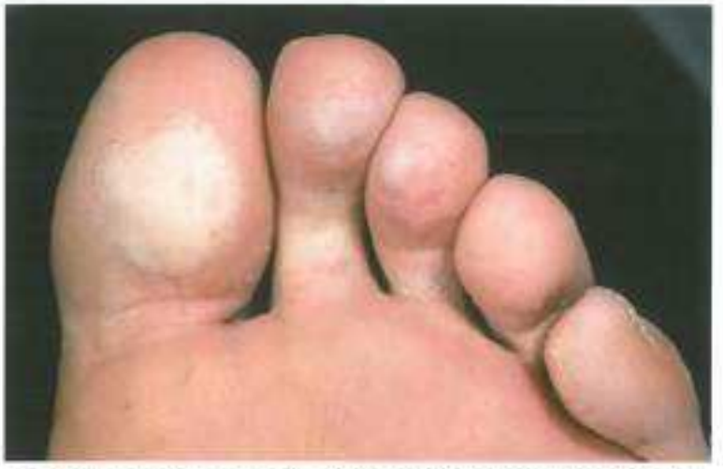


Fig. 24.56 Pitted keratolysis. The stratum corneum becomes macerated and sodden with hyperhidrosis. Occlusive footwear accentuates the problem. (Courtesy of Dr A. C. Pembroke).

- **Surgical excision of axillary skin** This is an excellent treatment for those disabled by axillary hyperhidrosis. The main sweat-producing area of axillary skin is excised. The procedure is uncomfortable post-operatively and secondary infection may occur. The resulting scars are unsightly but not usually disturbing to the patient.
- **Oral anticholinergic drugs** Ocular and intestinal side-effects restrict their use; however oral glycopyrrolate is sometimes helpful.
- **Tranquillizers** Doses that induce drowsiness are relatively effective in reducing the emotional triggers, but the side-effects inhibit their usefulness.
- **Botulinum toxin type A (Botox)** Local injections inhibit the release of acetylcholine from the presynaptic membrane of cholinergic neurons and are helpful at inducing temporary remissions in palmar (although temporary paralysis of the small muscles of the hand may occur) and axillary hyperhidrosis.

PITTED KERATOLYSIS

Pitted erosions of the stratum corneum caused by infection with coryneform bacteria and other species associated with hyperhidrosis.

Aetiology

Keratolysis plantare sulcatum occurs in patients who have considerable hyperhidrosis of the feet. Occlusive footwear causes the skin to become damp and sodden. The macerated stratum corneum is invaded by organisms. The coryneform species *Micrococcus sedentarius* and filamentous bacteria are found in the pits. The coryneforms produce proteolytic enzymes that digest keratin and leave the crateriform pits.

Clinical Features

Symptoms

There may be none but occasionally there is an odour.

Morphology

Circular, superficial, punched-out and irregular erosions occur symmetrically (Fig. 24.55).

Distribution

The weight-bearing areas of the soles and toes (Fig. 24.56).

Management

The organisms may be found in Gram-stained scrapings. Treatment of the hyperhidrosis is necessary; 30% formalin soaks are helpful. Topical fucidin, clotrimazole or systemic erythromycin may eradicate the organisms.

The differential diagnosis is *aquagenic wrinkling of the palms*, where there is rapid onset of transient white oedematous plaques on the palms shortly after exposure to water. Most cases are idiopathic, but marasmus, rofecoxib and cystic fibrosis may be responsible, probably due to increased epidermal salt concentration.

Body odour

Body odour results from bacterial decomposition of organic substances from the eccrine, sebaceous and apocrine glands into volatile compounds of low molecular weight. Each region has its own distinctive odour. Powerful foot odour is caused by short-chain fatty acids, for example isovaleric acid, which are odourless in the metallic salt form. However, it is not known why some subjects have problems with foot odour.

There is a rare inborn error of metabolism that results in a fishy odour that is perfectly apparent (*trimethylaminuria*). It results from a deficiency of hepatic trimethylamine oxidase such that di- and trimethylamine accumulates. These patients cannot degrade fish and the odour emanates from the breath and sweat.

Occasionally patients are convinced that they smell, but this is not apparent and they are usually deluded.

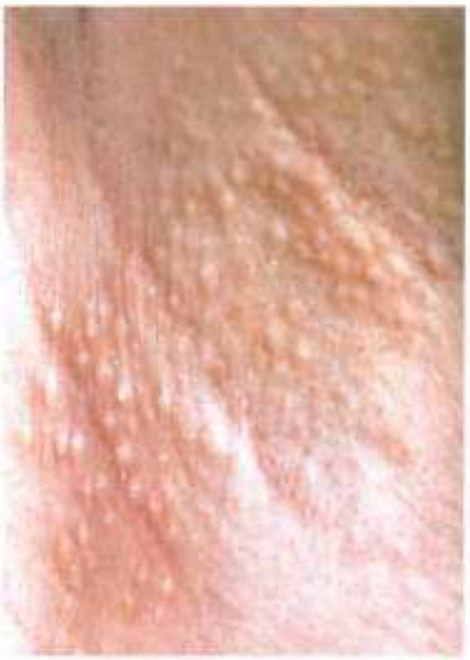


Fig. 24.57 Fox–Fordyce disease. Itchy, skin-coloured or pigmented, small, dome-shaped follicular papules occur, primarily in the axillae, as a result of the retention of apocrine secretions.

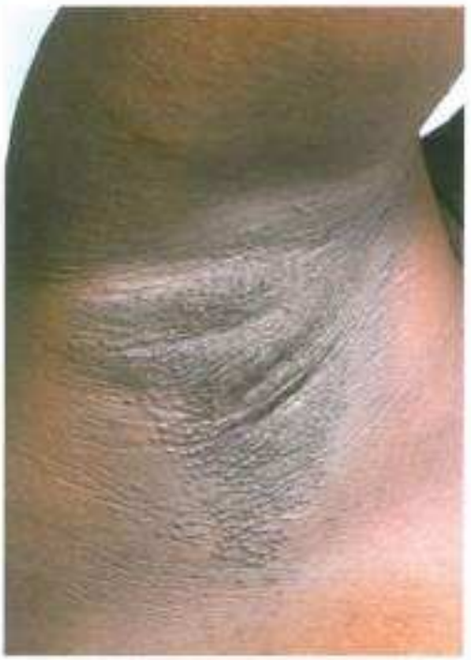


Fig. 24.58 Fox–Fordyce disease. Flesh-coloured, pruritic, dome-shaped papules are present in the axillae. Surgical excision is sometimes necessary.

Disorders of the apocrine glands

FOX–FORDYCE DISEASE (APOCRINE MILIARIA)

Apocrine sweat retention and inflammation following blockage of the apocrine ducts.

Aetiology

The cause is unknown but it is seen most commonly in women, particularly after puberty, sometimes persisting through to the menopause. It often remits during pregnancy and hormonal factors may be relevant. Pathologically, there is follicular plugging with infundibular acanthosis, parakeratosis and spongiosis with a non-specific infiltrate and occasionally sweat retention vesicles and a specific peri-infundibular and ductal infiltrate of xanthomatized cells.

Clinical Features

Symptoms

Pruritus, often precipitated by emotion that causes apocrine secretion.

Morphology

There are skin-coloured, dome-shaped, follicular papules (Figs 24.57 and 24.58).

Distribution

Axillae primarily but sometimes around the breasts and anogenital area.

Management

Unsatisfactory but topical steroids, local ultraviolet light and oral contraceptives may be tried. Surgical excision is sometimes necessary.

Nail disorders 25

The nail consists of hard keratin formed from an invagination of the skin overlying the distal phalanx. It lies on a bed of epidermis to which it is firmly attached. It grows mainly from a matrix that is directly under the posterior nailfold and extends to the foremost portion of the lunula (half-moon). The half-moon is paler than the rest of the nail because keratinization is incomplete and possibly because the connective tissue is packed more loosely. There is no granular cell layer, the epithelium is thickened (therefore, the blood vessels are less obvious) and there is parakeratosis, which interferes with the passage of light. The lunula is enlarged in hyperthyroidism and reduced with age and in racquet nails. It is triangular in the nail patella syndrome. The cuticle is an extension of the stratum corneum of the skin, from the dorsal surface of the finger onto the nail plate. It plays an important role in sealing off the potential space between the roof of the nailfold and its floor. The nail acts as a protection to the underlying distal phalanx, facilitates the picking up of small objects and contributes to the appreciation of fine touch.

Under normal circumstances, the fingernails take about 5 months to grow out, and the toenails 12–18 months, which is why the fingernails require cutting more frequently. Individual nails differ slightly in their growth rates, and those on the dominant hand grow fastest. Nail growth is accelerated in psoriasis, a disorder of epidermal proliferation, and decreased in severe illness or in ischaemic states.

The diagnosis of nail disorders is no more difficult than that of skin disorders, but the physical signs must be elicited.

- **Pitting** Pits are small depressions in the nail plate, which may be scattered or arranged in lines. Common causes include alopecia areata, psoriasis, eczema and the twenty nail dystrophy of childhood.
- **Onycholysis** This is separation of the nail away from the nailbed. Common causes include psoriasis, tinea, thyrotoxicosis and phototoxicity.
- **Ridging of the nails** Visible horizontal or vertical lines result from a disturbance in nail growth. Causes of horizontal ridging include Beau's lines and inflammatory disorders affecting the nailfolds such as eczema and candidal infection. Vertical lines may be the result of a median nail dystrophy or a habit tic.
- **Thickening of the nail plate** This results from a disease process involving the nailbed such as psoriasis or tinea.
- **Abnormally curved nails** Koilonychia, clubbing, ingrowing toenails and onychogryphosis are common causes.
- **Disturbances of colour** There are a number of colour changes, for example, white (trauma, tinea, liver and renal disease), yellow (psoriasis, tinea, yellow nail syndrome), green (*pseudomonas*), brown (*Candida* sp., linear melanonychia, external staining), black (malignant melanoma, tinea, trauma) and red-brown (trauma).

There is an understandable tendency to regard every abnormality as fungal in origin and to treat accordingly, which is admirable in one sense because fungal disorders are treatable, but this may not be the correct diagnosis. It is therefore wise to take clippings and have the diagnosis of a fungal disorder established in the laboratory before commencing a potentially toxic and often protracted therapy.

Nail infections

ACUTE PARONYCHIA

An acute, bacterial infection of the lateral or posterior fingernails.

Aetiology

The organism, which is usually *Staphylococcus aureus* but sometimes *Streptococcus pyogenes*, gains entry to the posterior or lateral nailfold either through a minor injury (sometimes secondary to nail biting), or into an already damaged nail. In the latter, *Pseudomonas aeruginosa* (*Ps. pyocynea*) is often involved. Sometimes the infection may develop deep under the nail plate.

Clinical Features

Symptoms

The condition is acute in onset and painful.

Morphology

If it involves the nailfolds, the infection may be quite superficial and the pus is evident (Fig. 25.1). Alternatively, it may be deeper and a red, tender

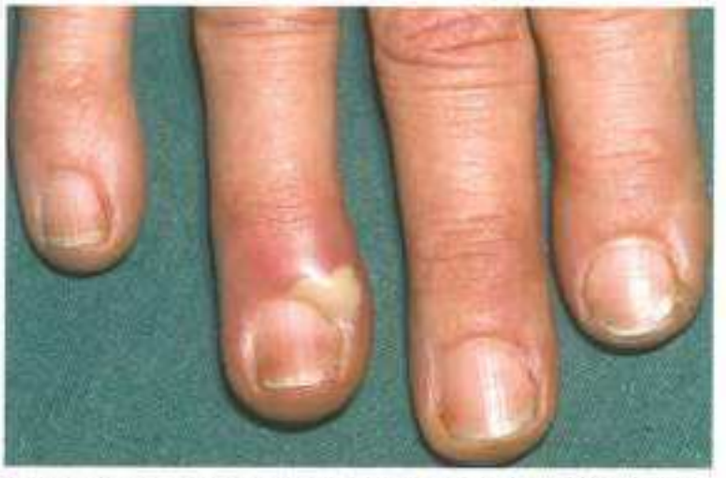


Fig. 25.1 Acute paronychia. The condition is acute and painful. Pus is evident with surrounding inflammation and *Staphylococcus aureus* is usually the cause.

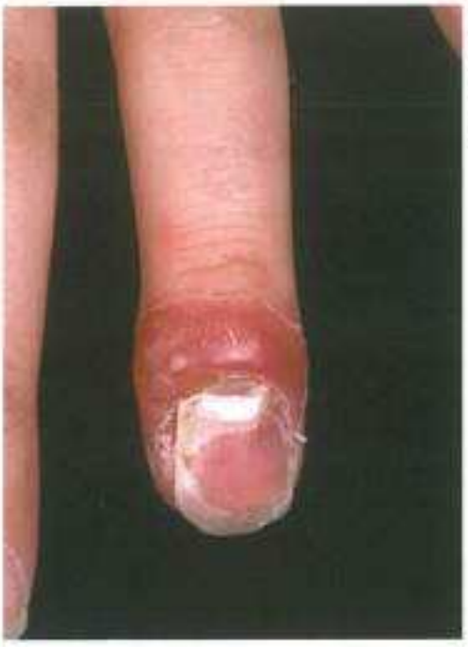


Fig. 25.2 Acute paronychia. If the infection is deeper, there is a red tender swelling around and under the nail.

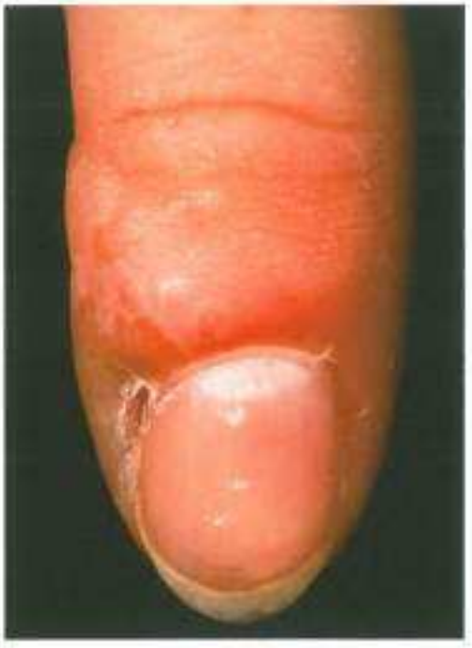


Fig. 25.3 Herpetic whitlow. There are vesicles and oedema adjacent to the fingernail. This nurse had been attending to a patient with active herpes simplex.

swelling is present around the nail (Fig. 25.2). If the infection is underneath the nail, the nail plate becomes loose and distorted, and it may be lifted off to reveal purulent material.

Distribution

Only one nail is normally involved.

Management

The diagnosis is not difficult but the differential diagnosis includes a *herpes simplex whitlow* (Fig. 25.3), where there are vesicles surrounded by erythema. In the early stages of the infection, an antibiotic, such as flucloxacillin 250 mg four times daily for a week, may be effective. Pus from superficial infections can be released by incision but may require surgical drainage if deeper. For infections underneath the nail, the nail may need to be removed.

CHRONIC PARONYCHIA

A chronic infection, usually secondary to *Candida albicans*, that involves the posterior or lateral nailfolds of the fingers, and ultimately the nail itself.

Aetiology

The condition is common, affects women more than men and is occupational. Frequent immersion of the hands in water (by housewives, nurses, barmaids, chefs, hairdressers, for example) softens and eventually destroys the cuticle, permitting the commensal and opportunistic organism *C. albicans* to enter and flourish in the damp and occluded microenvironment under the nailfold and subsequently invade the nail plate. Occasionally, the patient also has diabetes mellitus or vaginal candidiasis or pushes the cuticles back too enthusiastically.

C. albicans is the most common cause but *Candida parapsilosis* and *guilliermondii* may also be involved. Very much less commonly, primary invasion of the nail plate may occur without preceding paronychia. Gross infections occur as part of *chronic mucocutaneous candidiasis*, which involves the mouth, skin and nails beginning in infancy or childhood. If there is systemic involvement, there may be an underlying immunodeficiency such as severe combined deficiency, but in the localized varieties the precise defect of immune function is not yet fully understood. There are usually other infections including warts and dermatophytosis, and the conditions may be inherited as an autosomal dominant or recessive. It may occur with the *polyendocrinopathy syndrome*, especially with hypoparathyroidism and hypoadrenocorticalism, and sometimes with pernicious anaemia, ovarian failure, hypothyroidism, vitiligo and alopecia areata. Occasionally it occurs with hypothyroidism alone, and there is a late-onset form of chronic mucocutaneous candidiasis associated particularly with a thymoma (see also Ch. 15).

Clinical Features

Symptoms

The patient complains of a swelling around the nail and observes that a small bead of pus discharges from time to time. The condition is not uncomfortable unless an acute bacterial infection supervenes. The nail may become discoloured.

Morphology

There is a red, sometimes boggy, swelling (Figs 25.4 and 25.5) of the posterior and lateral nailfolds. The cuticle is absent and a gap is visible between the nailfold and the nail plate.

Later, the nail growth is affected by horizontal cross-ridging. This is secondary to involvement of the nail matrix under the nailfold. The nail plate itself may become invaded and discoloured brown (Fig. 25.6) by *C. albicans* or green by *Ps. aeruginosa*.

Distribution

The index or middle finger is most commonly affected, although in neglected cases more than one fingernail is involved. Toenails may be involved in Muslims, who are required to wash their feet frequently as part of their religious ritual.

In primary candidosis of the nail plate, several nails are usually involved. In chronic mucocutaneous candidosis (Fig. 25.7), in addition to the gross nail dystrophy there is swelling of the nailfolds, which may be absent in the *candidal endocrinopathy syndrome* (Figs 25.8 and 25.9).

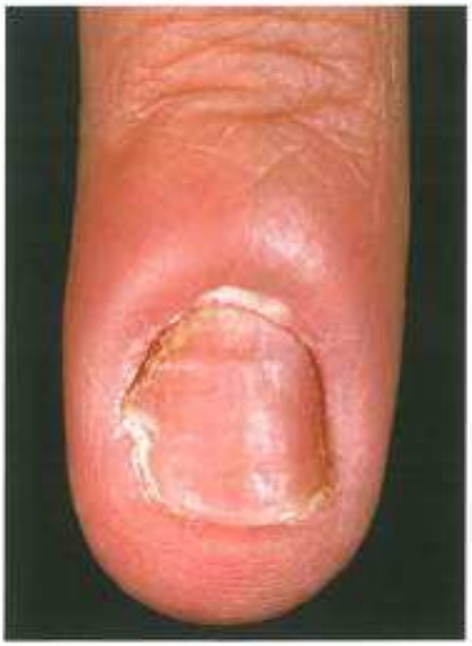


Fig. 25.4 Chronic paronychia. There is loss of the cuticle, oedema of the nailfolds and horizontal ridging of the nail.

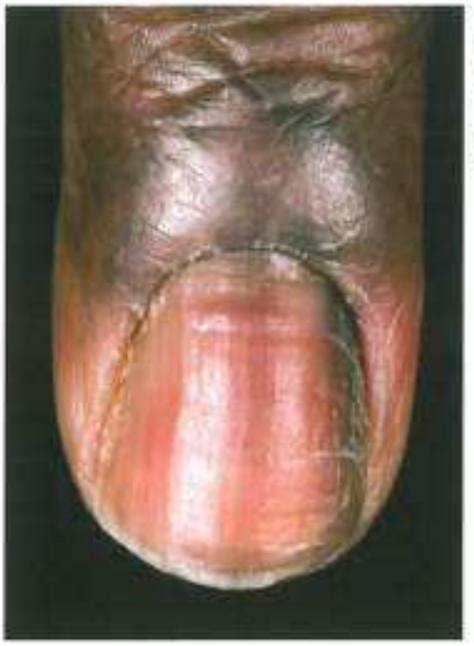


Fig. 25.5 Chronic paronychia. There is a shiny swelling of the posterior nailfold, loss of the cuticle and a discoloured dystrophic nail.

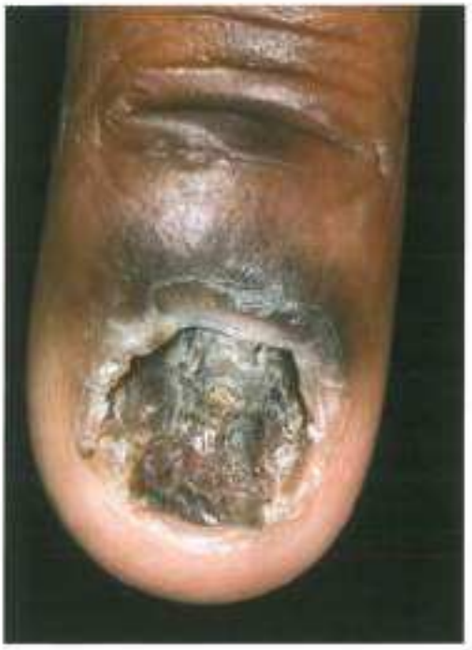


Fig. 25.6 Chronic paronychia. The nail plate may be invaded by *Candida albicans* and become discoloured and distorted. Note the bolstering of the nailfold and absent cuticle. Oral itraconazole is required.

Fig. 25.7 Chronic mucocutaneous candidosis. Persistent nailfold erythema and oedema, together with severe dystrophic changes in the nails, follow colonization by *Candida* sp. as a result of immunoparesis. (Courtesy of the Institute of Dermatology.)

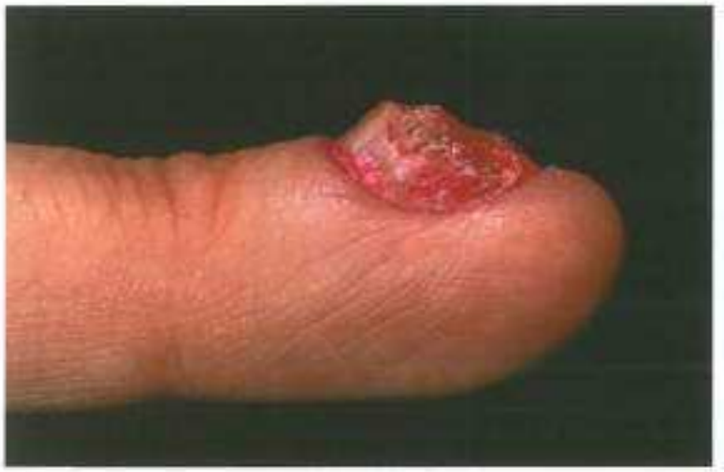


Fig. 25.8 *Candida* endocrinopathy syndrome. This woman has hypoparathyroidism. Her nails are thickened and dystrophic. The nailfolds are normal.

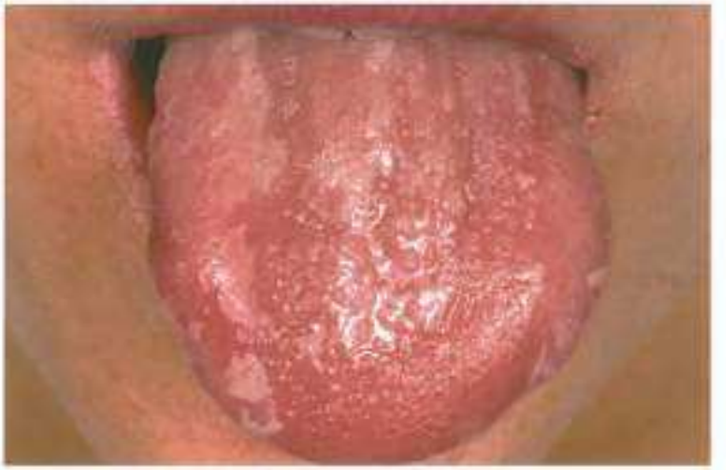


Fig. 25.9 *Candida* endocrinopathy syndrome. This patient with hypoparathyroidism (Fig. 25.8) also had chronic candidiasis in the mouth.

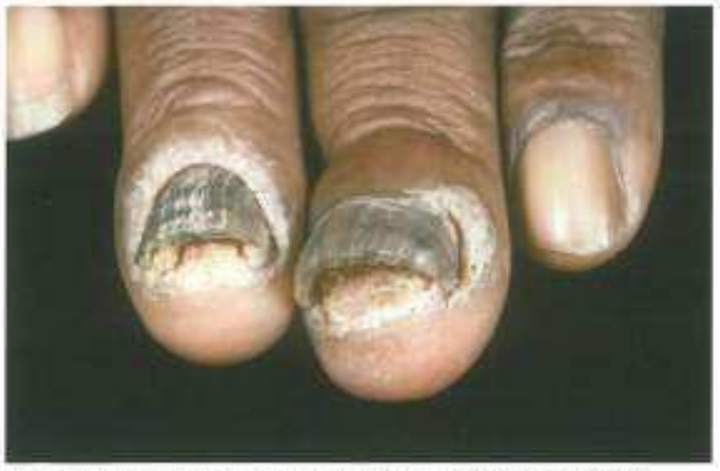


Fig. 25.10 Candidal infection of the nail plate. Brown discoloration and onycholysis are present in addition to swelling of the nailfold in this neglected case.

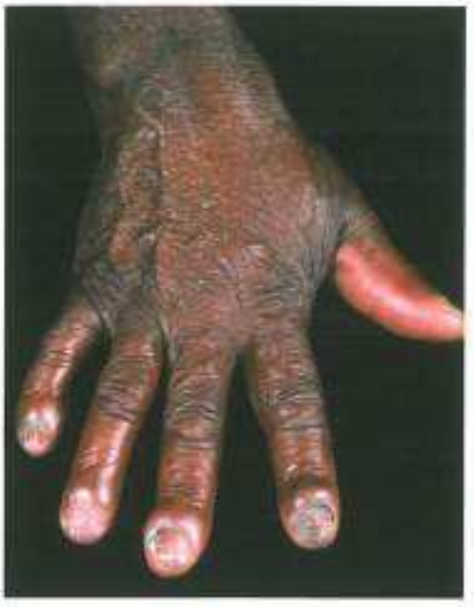


Fig. 25.11 *Candida parapsilosis*. The clinical appearances are similar to other Candida species. Several nails and nailfolds are involved.

Management

Successful management depends on convincing the patient of the significance of water. It is necessary to keep the skin dry. Plaster dressings are not helpful for they only increase the damp environment. Rubber gloves should be avoided because the hands and nails will become damp. If gloves are worn, cotton-lined ones are preferred for short periods only. Hand-washing, preparation and cleaning of vegetables, laundry, washing up (other family members can do this) and manicuring should be disallowed or minimized to deprive the microorganism of its ideal wet environment and to allow the cuticle to reform.

The use of topical imidazoles on the nailfolds (but not under the nail, because this will prevent the reformation of the cuticle) are effective. The condition takes time to recover. Photographs or drawings are helpful to record progress.

If the nail plate is discoloured (Fig. 25.10), clippings should be taken for mycology and sensitivity (*Candida krusei* and *C. glabrata* are not sensitive to fluconazole). If *Candida albicans, parapsilosis* (Fig. 25.11) or *guilliermondii* are present, itraconazole (Sporanox) 100 mg daily (Figs 25.12 and 25.13) or in a pulse regime of 200 mg twice daily for one week per month for 3–4 months is indicated. Fluconazole 50 mg daily or terbinafine (Lamisil) 250 mg daily are alternatives. Chronic paronychia is frequently mismanaged. It is important to emphasize that griseofulvin is ineffective against *Candida* sp., that antibiotics are not appropriate unless bacterial sepsis has supervened and that surgical incision is not indicated. Diabetes mellitus should be excluded. The appropriate investigations should be instituted if immunodeficiency or associated endocrinopathy is suspected.

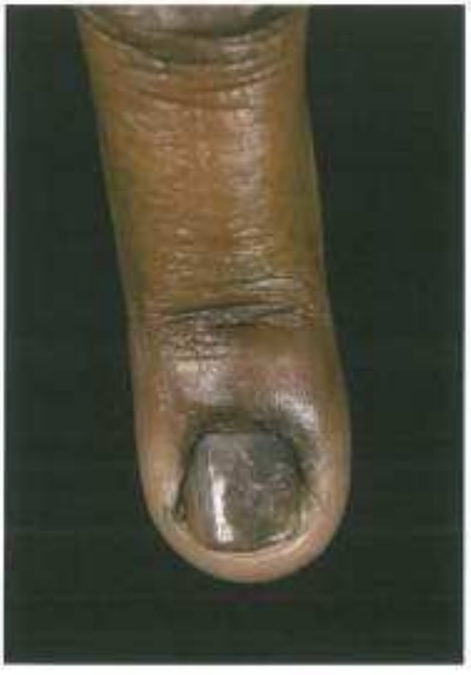


Fig. 25.12 Chronic paronychia. There is swelling of the posterior nailfold and discoloration of the nail plate from involvement by Candida sp.

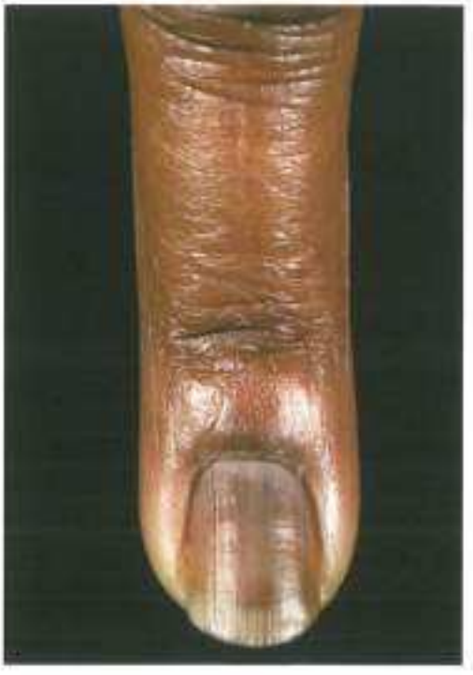


Fig. 25.13 Chronic paronychia. She was a baker and continually had her hands in water. The nail (Fig. 25.12) was treated for 3 months with itraconazole and was completely healed 6 months later.

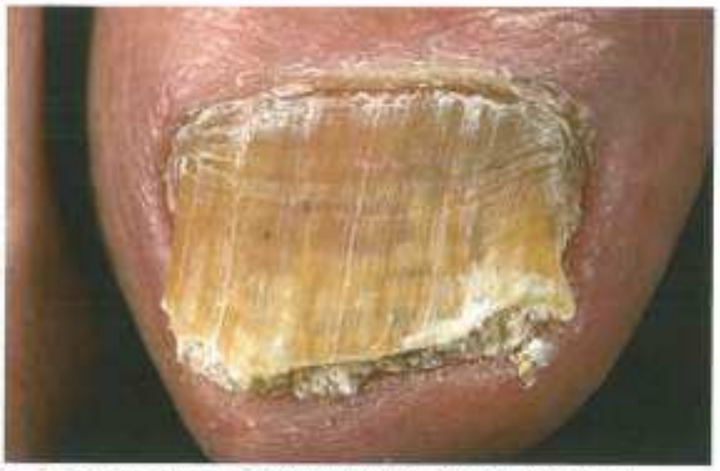


Fig. 25.14 Tinea unguium. The nail becomes thickened distally and soft hyperkeratotic material is present underneath it. The nail is discoloured yellow.

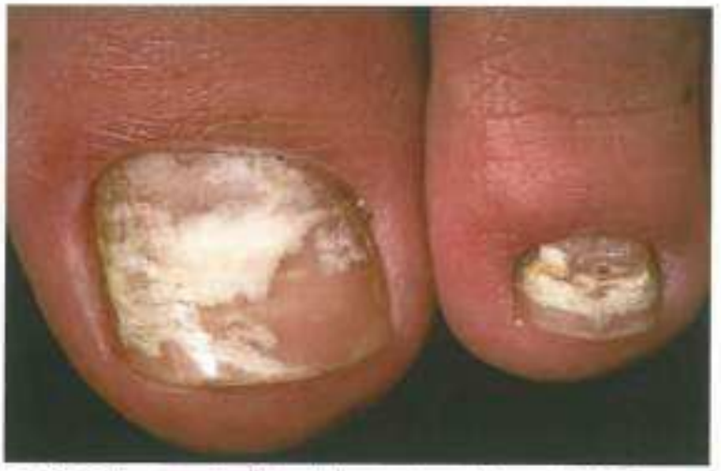


Fig. 25.15 Tinea unguium. *Trichophyton mentagrophytes* var. *interdigitale* produces a superficial white discoloration of the nail.

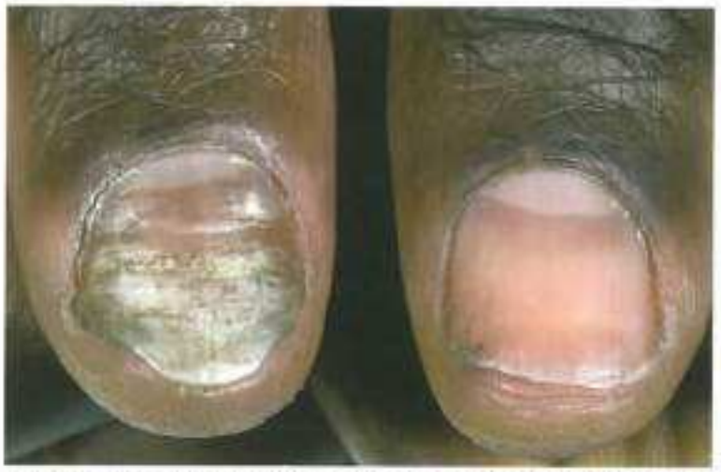


Fig. 25.16 Tinea unguium. Tinea tends to be asymmetrical. Often the fingernails or thumbnails of one hand only are affected.

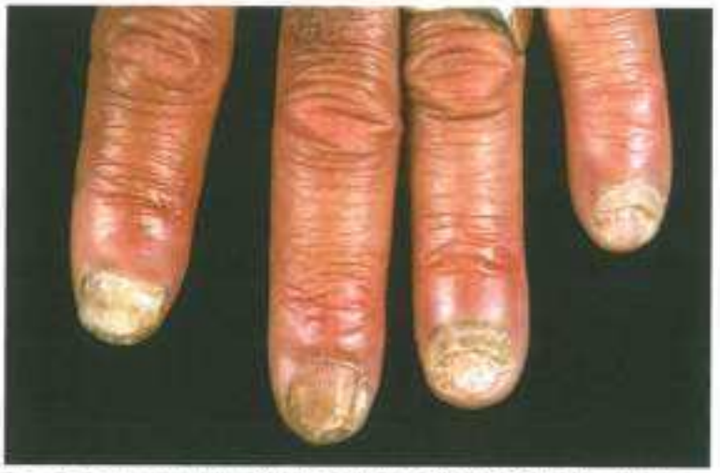


Fig. 25.17 Tinea unguium. Only one hand was affected. This is characteristic. The individual nails are involved to a varying degree, some more than others.

TINEA UNGUIUM

An infection of the nail plate with a dermatophyte.

Aetiology

Trichophyton rubrum and *T. mentagrophytes* var. *interdigitale* are the common causes. *Epidermophyton floccosum* rarely infects the nails. It usually begins in the skin as tinea pedis. There is subsequent infection of the toenails and occasionally it spreads to the skin of one hand and thence to the fingernails. It is unusual for fingernails to be infected without involvement of the toenails (except in children). The fungus enters either from the lateral nail-fold or from the nailbed. Many patients have a cool peripheral circulation. Patients with human immunodeficiency virus are particularly prone to *T. mentagrophytes*.

Clinical Features

Symptoms

Discoloration and thickening of the nails.

Morphology

The sides of the nails are affected initially and are discoloured yellow, brown or white. Subsequently, the nailbed becomes thickened distally (Fig. 25.14) and the nail plate is crumbly, which is apparent when taking clippings for mycology. The nailbed is composed of a soft hyperkeratotic material that can be scraped out with a blunt scalpel. As invasion spreads, the whole nail and its bed become thickened, discoloured and distorted. The nail may separate from its bed, causing onycholysis, and may break away altogether, resulting in complete destruction of the nail. *T. mentagrophytes* var. *interdigitale* produces a superficial white discoloration of the nails (Fig. 25.15).

Distribution

The distribution is asymmetrical (Fig. 25.16) with variable involvement of the nails. The nails of one foot may be involved more than the other, and the corresponding toe on the other foot may be either uninvolved or only affected to a limited degree. The fingernails (Fig. 25.17) of one hand may be involved for many years before, if ever, spread occurs to the other.

Management

It is important to take generous clippings of the nail and of the subungual hyperkeratosis for mycology. The samples need to be soaked in potash for some hours for direct microscopy, and even then identification of the hyphae is not easy. The fungus should grow on culture. Clippings are always worth repeating, if the tests are negative.

Sometimes fungal hyphae are seen on direct microscopy but nothing grows on culture. This may be because the infection is with *Scytalidium dimidiatum* or its non-pigmented variety *S. hyalinum* (Fig. 25.18), which is

Fig. 25.18 *Scytalidium hyalinum*. This infection is common in Afro-Caribbean patients. Fungal hyphae are seen on direct microscopy but no organism is cultured unless cycloheximide is omitted from the culture medium.

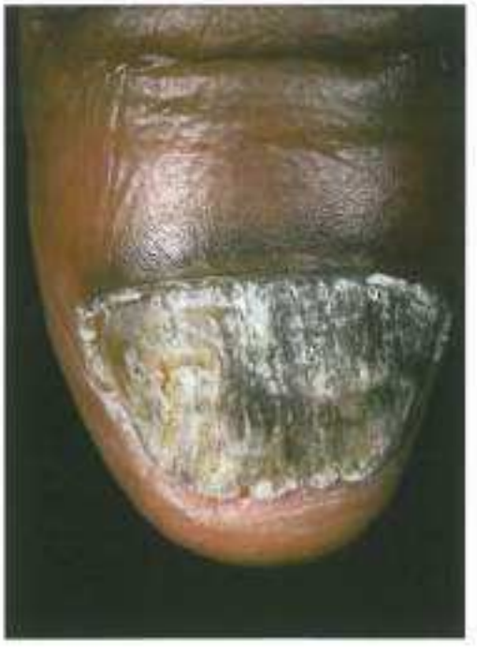


Fig. 25.19 *Scytalidium hyalinum*. The appearance can be very similar to that of *Trichophyton rubrum* infection but it does not respond to current antifungal drugs.

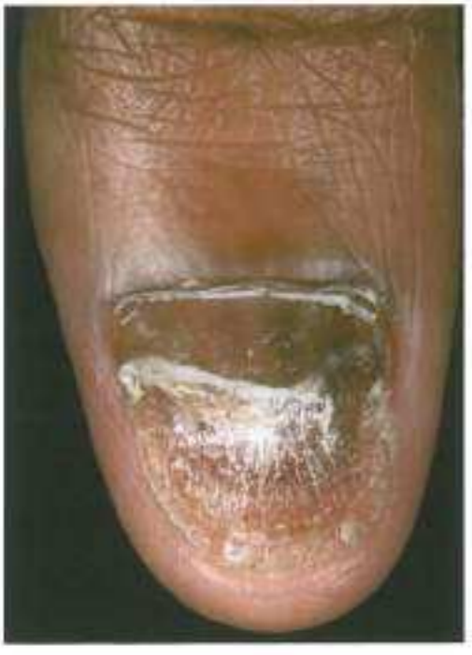


Fig. 25.20 Tinea unguium. The thumbnail is thickened and discoloured and the distal portion has broken off. Nail clippings were positive for *Trichophyton rubrum*.

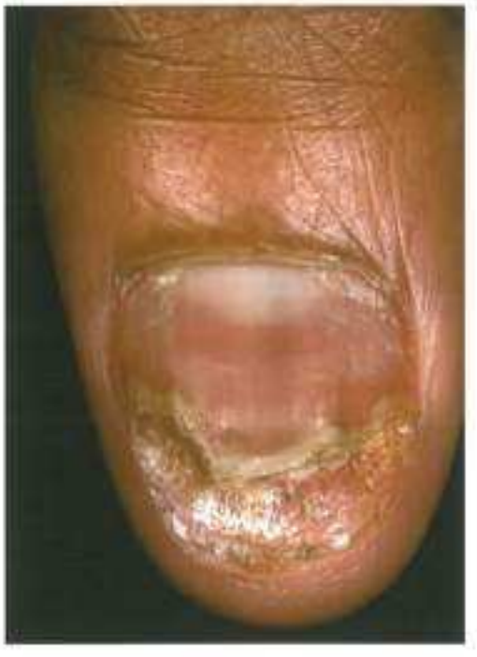


Fig. 25.21 Tinea unguium. The nail is shown during recovery after 2 months of griseofulvin. Terbinafine orally is now the drug of choice.

endemic in the Caribbean, West Africa and Thailand. The clinical features are similar (Fig. 25.19) but treatment is unsatisfactory at present.

Tinea of the nails responds to many months of systemic therapy (Figs 25.20 and 25.21). The diagnosis should be proven before treatment, which would be fruitless if mycology is negative. It is always worthwhile treating fingernail infections as they will clear within 6 months, but toenail infections take longer and one cannot guarantee cure in older patients where their nails grow more slowly.

Terbinafine is fungicidal and has superceded griseofulvin. It is distributed into the nail plate within a few weeks and the drug is taken for 3 to 4 months. Itraconazole (Sporanox) may be taken in a pulse regimen of 400 mg twice daily for a week once a month for three to four pulses.

Topical therapies are not very effective but may increase the chances of cure if combined with a systemic agent. Claims have been made that surgical avulsion of the nail followed by topical agents may be effective. Topical drugs that are used include tioconazole, ketoconazole, amorolfine and ciclopirox.

PSEUDOMONAS INFECTIONS

Pseudomonas sp. are secondary invaders of an already abnormal nail.

Aetiology

Ps. pyocyanea is ubiquitous and is found in tap water. It is an opportunist in diseased nails, particularly in onycholysis and chronic paronychia.

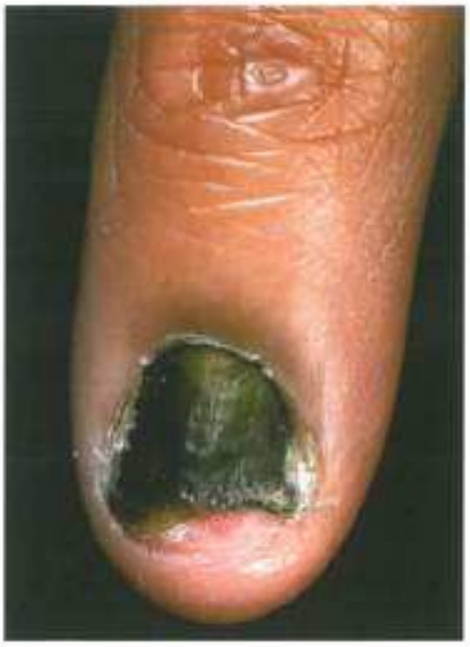


Fig. 25.22 *Pseudomonas* infection of the nail. The dark green discoloration is characteristic. The cuticle is softened and destroyed by water so causing a chronic paronychia, which is secondarily invaded by pseudomonas.

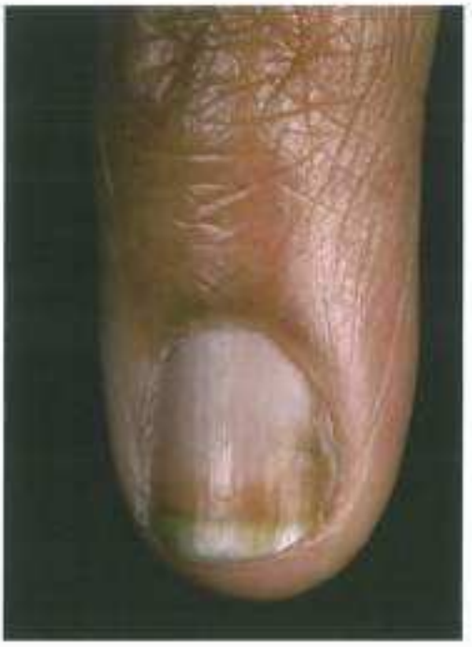


Fig. 25.23 Treated *Pseudomonas* infection of the nail. The infected nail (Fig. 25.22) responded to keeping the nail dry and painting with 15% sulphacetamide. 2% acetic acid is also effective.

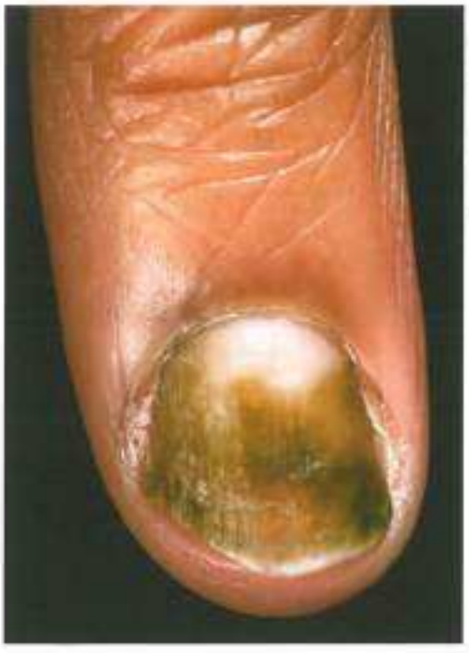


Fig. 25.24 *Pseudomonas* infection of the nail. This woman was a baker and her hands were continually wet. The green discoloration was caused by *Pseudomonas aeruginosa*.

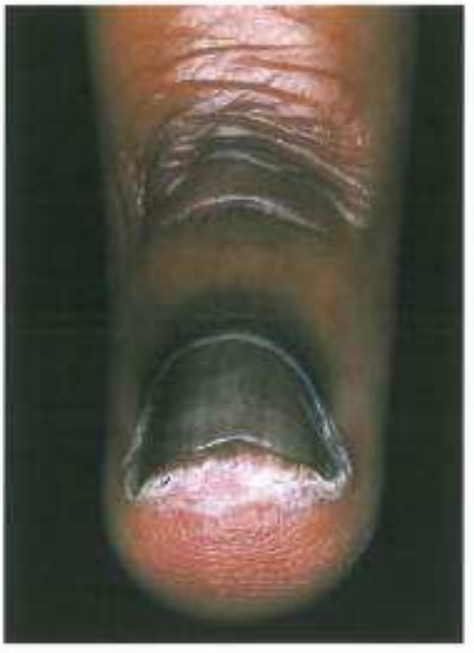


Fig. 25.25 *Fusarium* sp. infection. Non-dermatophyte moulds account for a minority of nail infections. They are usually unsuspected clinically and standard antifungals are not effective. *Fusarium* is only of pathological significance in severely immunocompromised individuals (e.g. acute myeloid leukaemia).

Clinical Features

Symptoms, morphology and distribution

There is a black, green (Fig. 25.22) or blue discoloration of the nail plate.

Management

Treatment is that of the primary condition. The superimposed *Pseudomonas* infection responds to 15% sulphacetamide in 50% spirit (30% sulphacetamide eye drops diluted by 50%) applied to the nailbed underneath the nails (Fig. 25.23). Mycology is always useful to differentiate pseudomonas infection (Fig. 25.24) from unsuspected microbes such as *Fusarium* sp. (Fig. 25.25) and *Aspergillus* sp. which may be grown on culture.

Inflammatory disorders of the nails

PSORIASIS OF THE NAILS

Involvement of the nails secondary to psoriasis.

Aetiology

Nail changes are common. Probably most psoriatic patients have them at some time. Nail changes may occur without evidence of cutaneous involvement, although the skin rash may appear years later or with minimal psoriasis elsewhere, classically on the scalp and the genitalia. Sometimes gross changes occur.

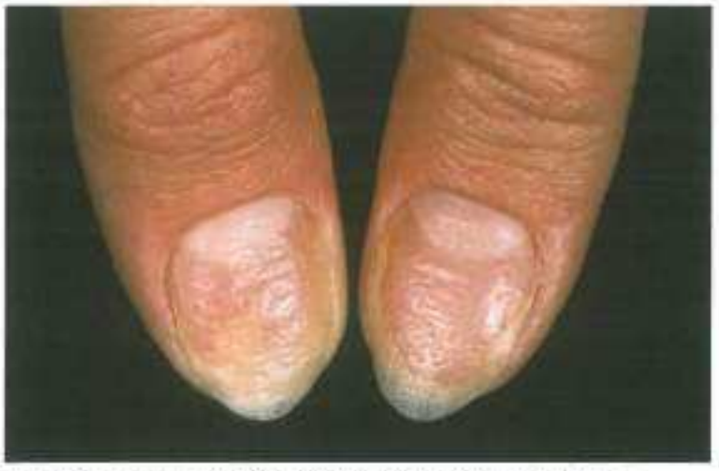


Fig. 25.26 Psoriasis. Parakeratotic areas in the nail are weaker than the surrounding nail and fall out to form pits.

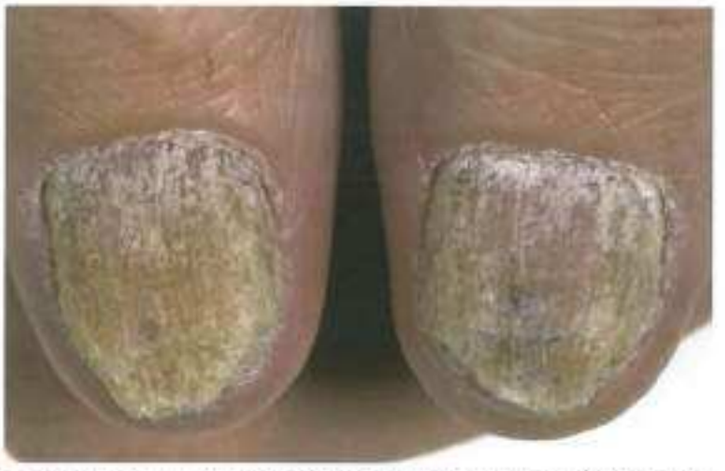


Fig. 25.27 Psoriasis. Pits may occur in a linear manner and produce longitudinal lines (sometimes known as trachyonychia) symmetrically.

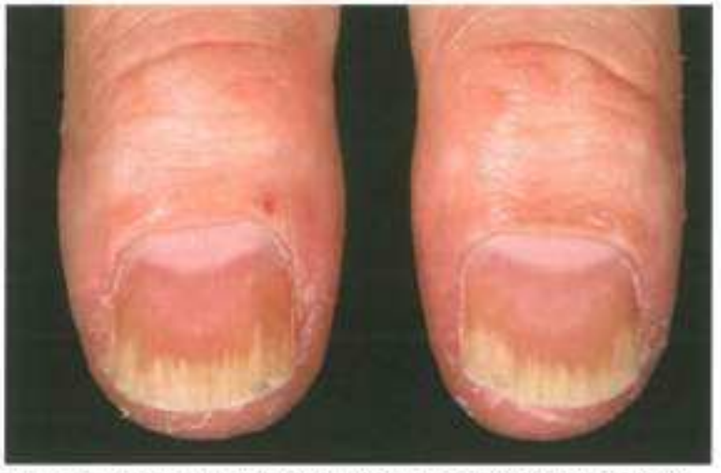


Fig. 25.28 Psoriasis. A yellow margin between the onycholysis and the normal nail is a particular feature of psoriatic onycholysis.

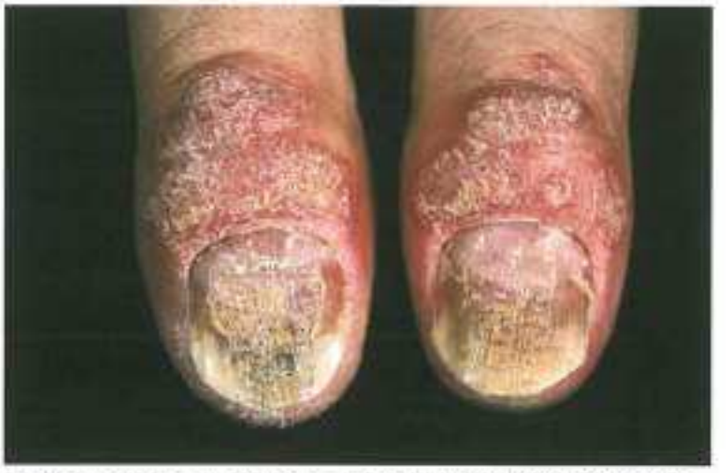


Fig. 25.29 Psoriasis and onycholysis. Here there is both psoriasis of the skin and onycholysis. Nail changes, however, may occur without the skin being involved at all.

Clinical Features

There are three main groups of abnormality.

- **Pitting** This is the commonest feature. The pits, which are usually minute, occur in a random or uniform pattern across the nail plate and may be arranged in lines (Fig. 25.26). The lunula itself is often involved. The changes are frequently symmetrical (Fig. 25.27). Pitting is thought to be caused by parakeratosis (retention of nuclei in nail keratin), similar to that which occurs in the stratum corneum in psoriatic skin. These areas of parakeratosis are presumed to be weaker than the surrounding nail and they fall out to leave the pits. The parakeratosis results from the hyperproliferation that occurs in psoriasis, which leads to an immature epithelium and hence nuclear remnants in horny tissue. Pitting is not specific to psoriasis, and identical changes occur in alopecia areata.
- **Onycholysis** It usually involves the free edge of the nail and a gap is visible between the nail plate and its bed, but it can occur centrally. A characteristic feature that distinguishes psoriatic onycholysis is a yellow margin (Fig. 25.28) between the white, separated, free edge and the pink, healthy nail. The changes are usually symmetrical (Fig. 25.29) and pits may also be present (Fig. 25.30). The onset of the condition may be quite sudden. The disorder is thought to be caused by psoriasis involving the nailbed and this is sometimes visible underneath the lifted nail.
- **Gross psoriatic nail dystrophy** This type is secondary to psoriasis underneath the posterior nailfold and the lunula in the nail matrix. The nail lacks lustre, becomes opaque, thickened and discoloured. Symmetry (Fig. 25.31) distinguishes this type from fungal disorders, as all the nails are usually involved to some degree; but the situation is not static, with one nail recovering and then another deteriorating. Complete recovery is unusual. Patients with psoriatic arthropathy involving the distal joints often have this type of nail involvement (Fig. 25.32), but nail changes frequently occur without arthropathy. Gross changes particularly occur in the Hallopeau type of psoriasis, which is acral and often pustular, and may be associated with HIV infection (Fig. 25.33).

Management

Clippings should be taken for mycological examination because occasionally psoriatics also have tinea, which is treatable whereas psoriasis of the nails is difficult. Superpotent topical steroids, in scalp application form applied under the nail, may be tried for onycholysis. Matrix disorders do not respond to topical therapy but do to systemic therapy with methotrexate or etretinate (Figs 25.34 and 25.35), when given for extensive cutaneous disease. However, it is questionable whether this is justified for nail involvement only.

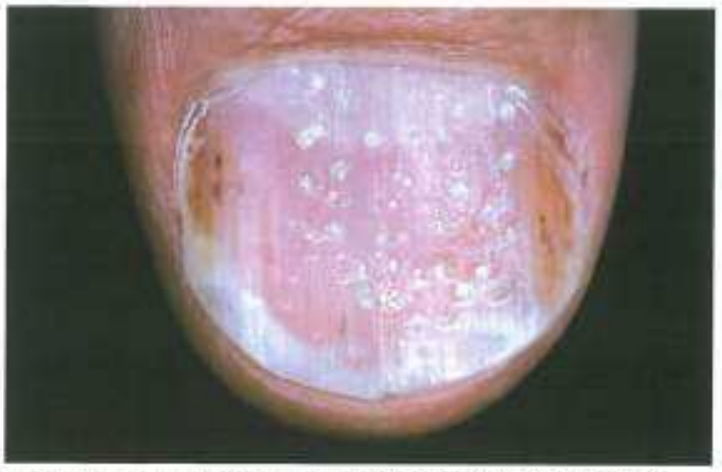


Fig. 25.30 Psoriasis. Onycholysis and pitting are common physical signs of psoriasis affecting the nails.

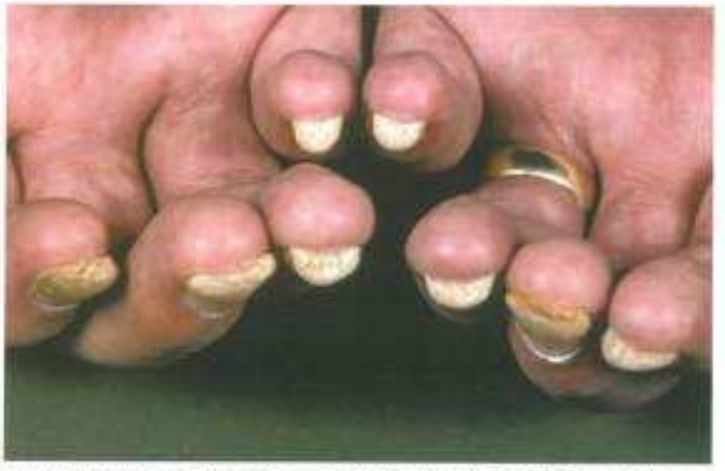


Fig. 25.31 Psoriasis. There is symmetrical hyperkeratotic psoriasis under the nails, which causes onycholysis.

Fig. 25.32 Psoriasis. Psoriasis is unusual in Afro-Caribbeans, and when it occurs the patient usually has Anglo-Saxon ancestry. These changes are gross and there is distal phalangeal arthropathy.

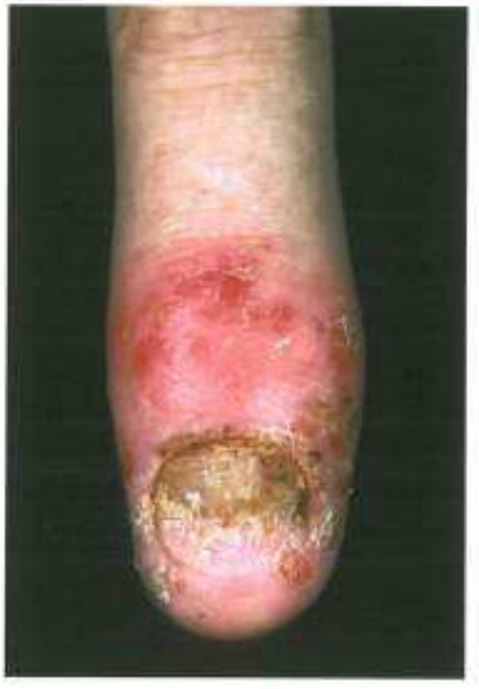
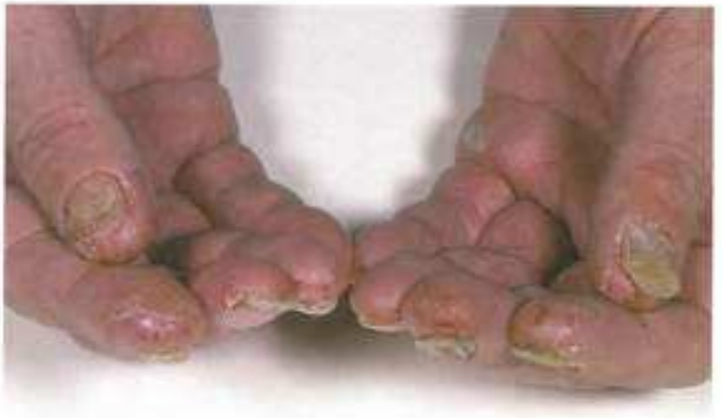
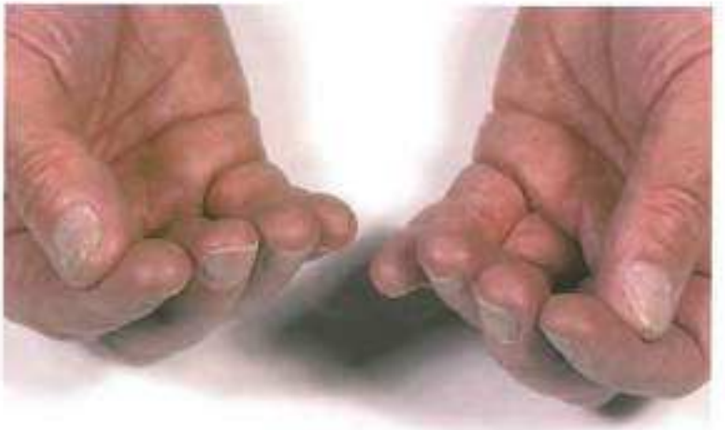


Fig. 25.33 Hallopeau psoriasis and onychodystrophy. There is distal phalangeal arthropathy and gross nail dystrophy. This patient was HIV-positive.





Figs 25.34 and 25.35 Psoriasis. Psoriasis of the fingertips (Fig. 25.34) is painful and does not respond well to topical therapy. This man's skin and nails were treated effectively with etretinate (Fig. 25.35).

LICHEN PLANUS

A disorder of the nail matrix caused by lichen planus.

Aetiology

Lichen planus is discussed elsewhere (Ch. 7). Nail changes occur only in a minority sometimes without cutaneous involvement, particularly in middle age. When present the changes can be severe and result in permanent damage. Similar changes occur in graft-versus-host disease (Fig. 18.117).

Clinical Features

Symptoms

The nails are abnormal.

Morphology

The common abnormality is an increase in the longitudinal lines (see Fig. 7.53), which develop into ridges because of thinning of the nail. Occasionally, as the nail plate becomes thin and atrophic (Fig. 25.36), the cuticle grows forward (see Fig. 7.54) onto the nail plate (known as a *pterygium*). The atrophic nail is then usually lost permanently (Fig. 25.37).

Distribution

One or several nails may be involved.

Management

Biopsy is helpful to establish the diagnosis (Fig. 25.38). Prednisolone in a dose of 0.5 mg/kg body weight daily for 3 weeks given early in the disease may prevent permanent scarring and loss of the nails, with recovery occurring within 3 months, but usually the diagnosis is made too late.

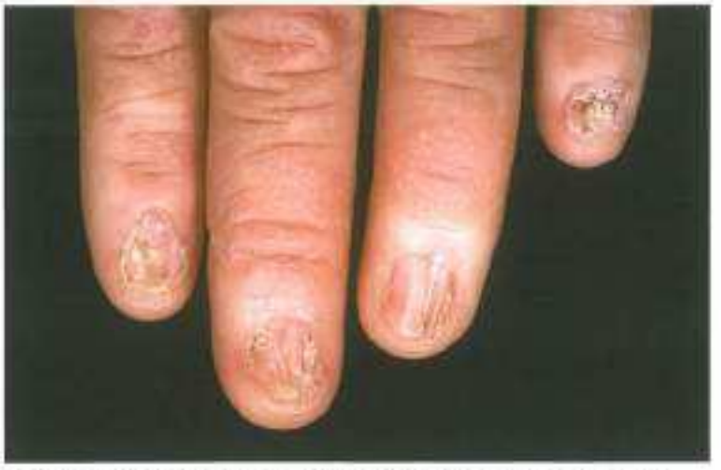


Fig. 25.36 Lichen planus. This patient came from Vietnam. The destruction tends to be permanent. There was still no recovery 7 years later.

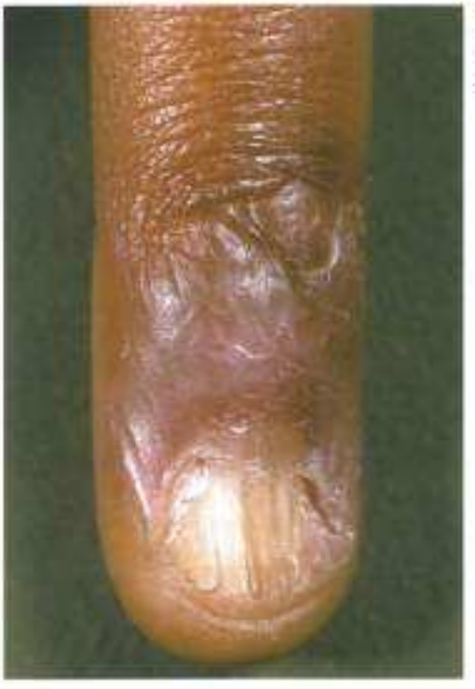


Fig. 25.37 Lichen planus. Permanent destruction of the nail may result.

ALOPECIA AREATA

Alopecia areata can cause nail abnormalities.

Aetiology

The cause of the nail changes is unknown but the aetiology of the hair changes is discussed in Chapter 26.

Clinical Features

Symptoms

None other than the appearance.

Morphology and distribution

Pitting occurs, often in a regular manner along either the longitudinal (Fig. 25.39) or the horizontal axis of the nail and sometimes both. Splitting may result. Many nails may be affected (Fig. 25.40). Occasionally gross changes occur, particularly in association with alopecia universalis.

Management

No treatment is available, but pitting usually disappears.

Fig. 25.38 Lichen planus. The diagnosis here was made by nail biopsy, an important part of management. Systemic steroids are the only treatment in the early stages.

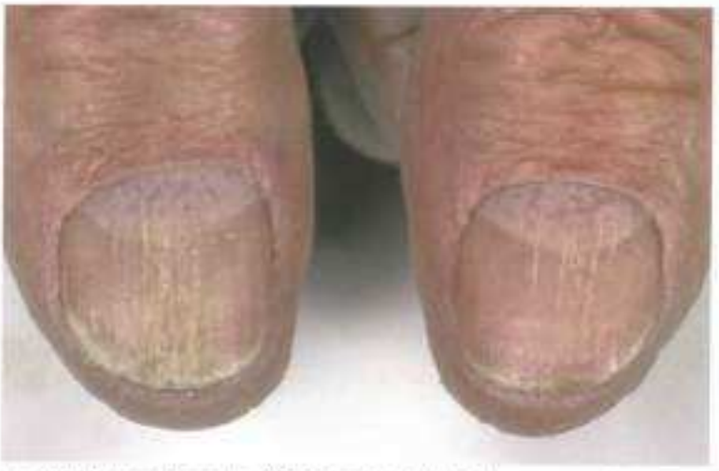


Fig. 25.39 Alopecia areata. A linear arrangement of pits may occur in a longitudinal manner, along the length of the nail. Note the pits in the lunulae.

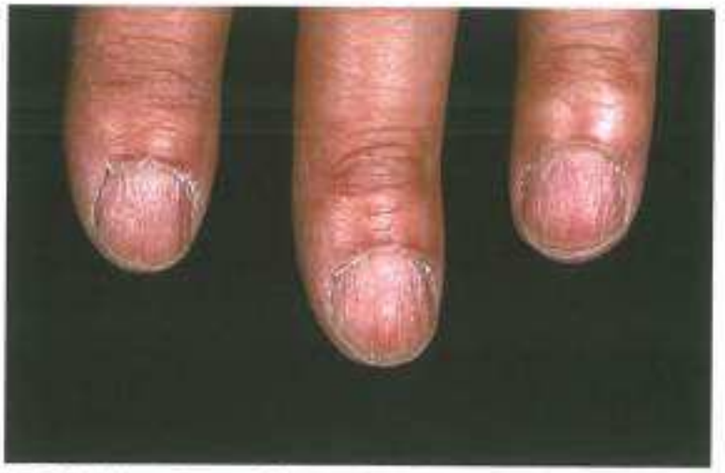


Fig. 25.40 Alopecia areata. Several nails may be affected with linear pitting. This man had alopecia universalis, where nail changes are common.

ECZEMA

Horizontal ridging of the nail secondary to eczema of the nailfold.

Aetiology

Eczema of the posterior nailfold disturbs the growth and development of the underlying nail matrix.

Clinical Features

Symptoms

A past or present history of eczema of the fingers may be obtained.

Morphology

Usually several horizontal ridges are present (Fig. 25.41). If the eczema has been severe, the nail or nails may be temporarily shed.

Distribution

One or more nails may be affected, depending on the degree of eczema.

Management

Treatment of the eczema on the skin stops the nail involvement. The ridging grows out over ensuing months.

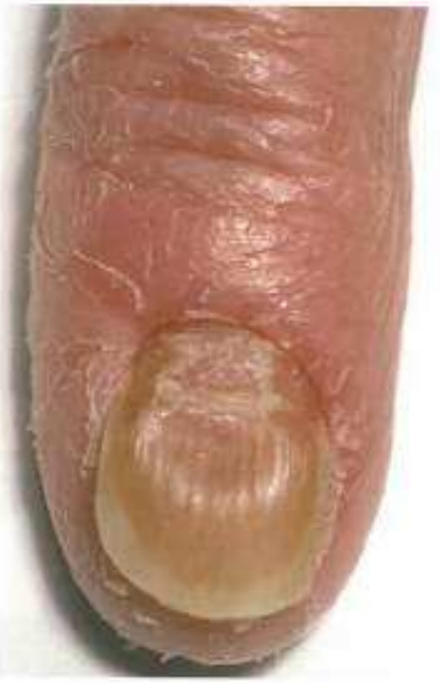


Fig. 25.41 Nail changes and eczema. Eczema around the nailfolds produces horizontal ridging and sometimes destruction of the nails.

TWENTY NAIL DYSTROPHY OF CHILDHOOD

A self-limiting childhood condition of excess ridging of all the nails.

Aetiology

The cause is unknown but it may be associated with autoimmune disorders including alopecia areata. It begins in infancy or childhood and ultimately resolves.

Clinical Features

Symptoms

A disturbance of all 20 nails.

Morphology

Ridging starts at the cuticle and progresses forwards to the tip of the nail.

Distribution

All 20 nails are affected (Fig. 25.42).

Management

There is no specific treatment, other than reassurance that the nails will recover.

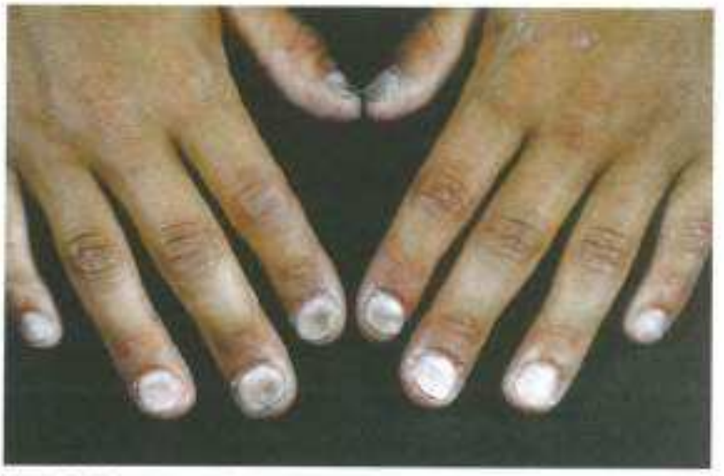


Fig. 25.42 The twenty nail syndrome. This is a disorder of all the nails that occurs in childhood. It usually resolves spontaneously.

PARAKERATOSIS PUSTULOSA

A nail disorder of childhood that results in hyperkeratosis under the free margin of the nail, possibly secondary to psoriasis or eczema.

Aetiology

It is more common in girls and often persists for several years.

Clinical Features

Symptoms

An abnormal nail in a child.

Morphology

There is striking hyperkeratosis under the free margin of the nail. The periungual skin may be pink and scaly (Fig. 25.43). The nail is lifted by this and deformed and thickened.

Distribution

It usually affects just one digit, often the thumb or index, but occasionally more. Sometimes the big toe can be affected.

Management

There is no specific treatment, although topical steroids are often used.

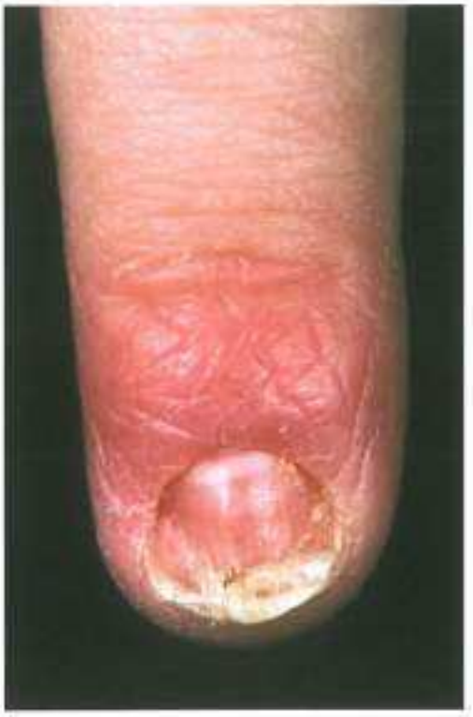


Fig. 25.43 Parakeratosis pustulosa. This 2-year-old boy had erythema and scaling surrounding the index finger, with hyperkeratosis and deformity of the nail. The condition resolves spontaneously with time.

Onycholysis of the nails

Onycholysis is separation of the nail from the nailbed.

Aetiology

The nail may separate away from its bed as a result of psoriasis, eczema, tinea or poor peripheral circulation. *Idiopathic onycholysis* (the most common type), is most often a result of trauma. It primarily occurs in females, presumably because women grow their nails long and the nail can be more easily detached by minor trauma.

If all the nails are involved, a systemic effect is likely, usually phototoxic but occasionally thyrotoxicosis. Phototoxic onycholysis is a reaction between intense ultraviolet light exposure and a photosensitizing drug (see Fig. 18.131). The drug is most commonly a tetracycline, especially the long-acting demethylchlortetracycline or doxycycline. A similar phenomenon was seen with the non-steroidal anti-inflammatory drug benoxaprofen (Opren). The widespread use of the photosensitizing chemicals 5- and 8-methoxypsoralen combined with ultraviolet A (PUVA) for the treatment of psoriasis and other skin diseases has led to an increase in iatrogenic photo-onycholysis.

Clinical Features

Symptoms

A visible abnormality without symptoms.

Fig. 25.44 Onycholysis. Loosening of the nail from the nailbed may occur without obvious cause.

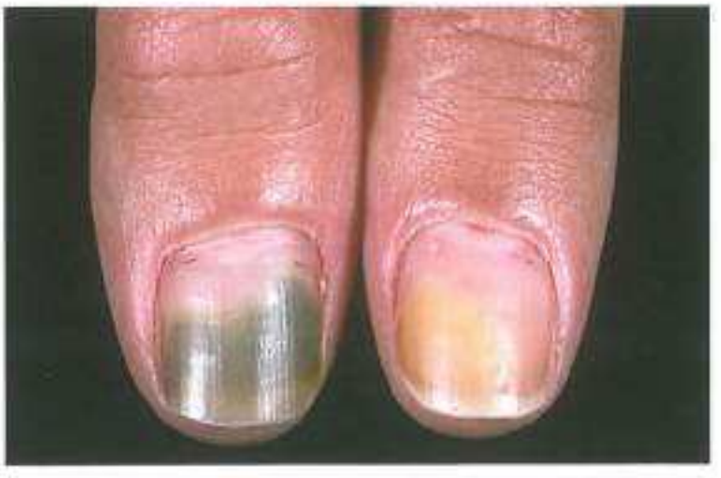


Fig. 25.45 Onycholysis. Minor trauma to long nails may cause onycholysis (right nail). *Pseudomonas aeruginosa* frequently invades and imparts a green colour (left nail).

Morphology
There is separation of the nail away from its bed, resulting in a white or cream discoloration (Fig. 25.44). Secondary bacterial infection with *Pseudomonas* sp. is not uncommon (Fig. 25.45).

Distribution
A single, several or sometimes all the fingernails may be affected.

Management
The cause, e.g. photo-onycholysis (Fig. 25.46) should be ascertained. Idiopathic onycholysis often resolves spontaneously. Secondary infection is the most common reason for the failure of the nail to reattach itself, coupled probably with further trauma. The nail should be kept clipped as short as possible to reduce further trauma, and the use of 15% sulphacetamide in 50% spirit is recommended as an antibacterial topical treatment.

Systemic causes of nail changes
Certain conditions cause little diagnostic difficulty and are well recognized by physicians and rarely present to a dermatologist. These include clubbing of the nails, where there is loss of the normal angulation between the posterior nailfold and the nail plate so that it is 180° or more (Fig. 25.47). The posterior nailfold, which overlies the nail matrix, feels spongy (Fig. 25.48). The distal phalanx enlarges as does the nail and its curvature becomes more pronounced. The causes of clubbing are pulmonary (carcinoma of the bronchus, bronchiectasis, tuberculosis, fibrosing alveolitis, asbestosis), cardiovascular (bacterial endocarditis, cyanotic congenital heart disease) and miscellaneous (cirrhosis, Crohn's disease, ulcerative colitis, thyrotoxicosis).

Splinter haemorrhages are tiny subungual haemorrhages (Fig. 25.49) that occur particularly in subacute bacterial endocarditis, systemic lupus erythematosus and trichinosis but are also very common secondary to trauma.

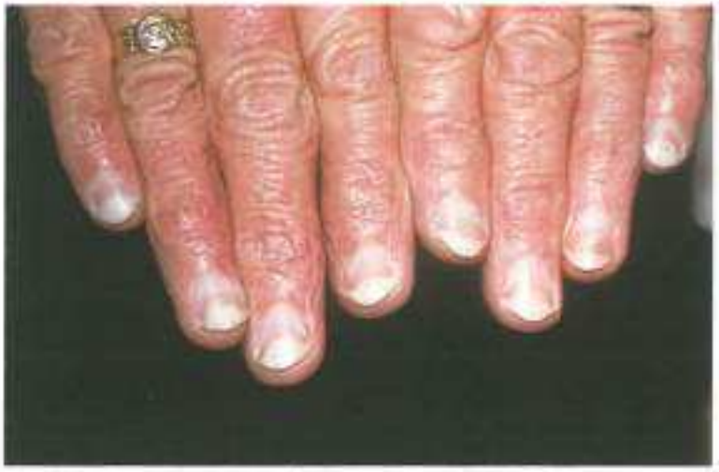


Fig. 25.46 Photo-onycholysis. Separation of the distal nail plate from the nailbed may occur after ultraviolet light irradiation and the ingestion of certain drugs. This patient had been taking benoxaprofen (now withdrawn).

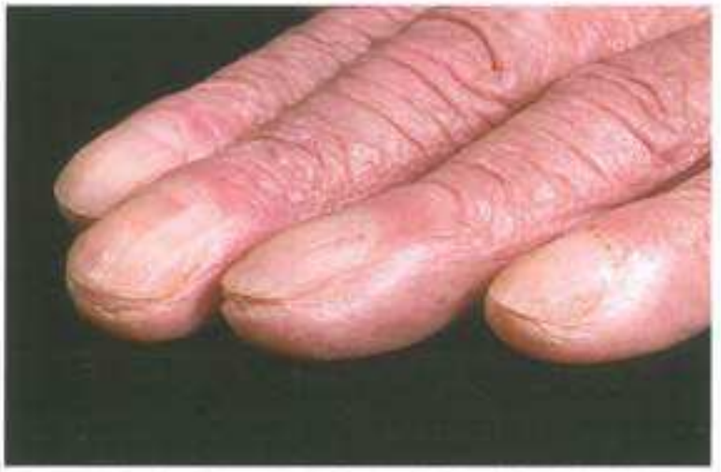


Fig. 25.47 Clubbing. The angle between the nailfold and the nail plate is 180° or greater. This man had lung cancer.

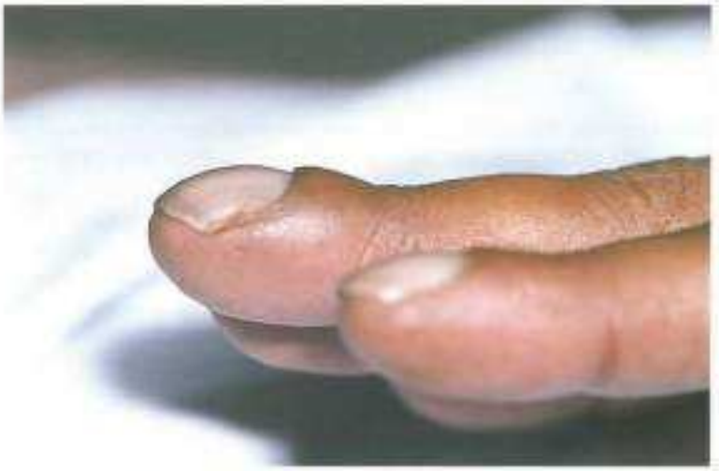


Fig. 25.48 Clubbing. There is loss of the normal angle between the nail plate and nailfold. The posterior nailfold feels spongy. The nail becomes more curved. This patient had pulmonary tuberculosis. (Courtesy of St Mary's Hospital.)

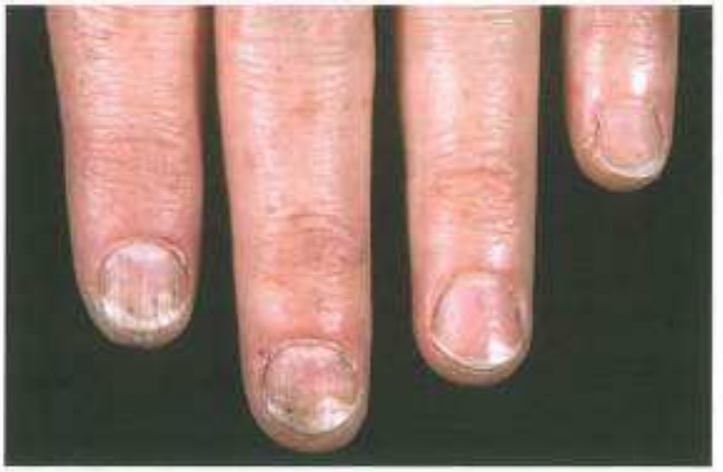


Fig. 25.49 Splinter haemorrhages. Tiny subungual haemorrhages result in pigmented, linear, splinter-like lesions. Trauma is the most common cause but they can also be a feature of certain systemic diseases.

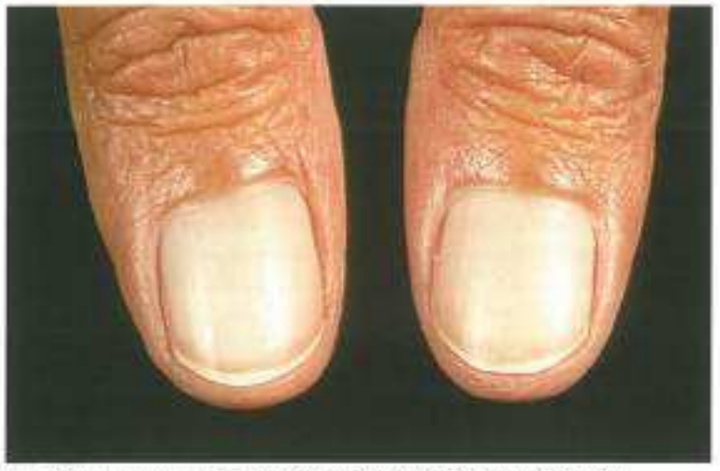


Fig. 25.50 Leuconychia. Horizontal broad white lines occur from hypoalbuminaemia. The whole nail may become white, as in this patient with cirrhosis.

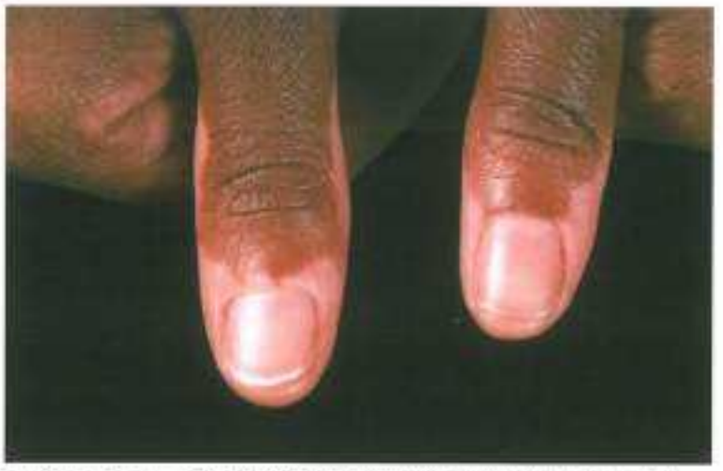


Fig. 25.51 Vitiligo. Fingertip vitiligo is common and unresponsive to treatment. The nailbed and surrounding skin are white.

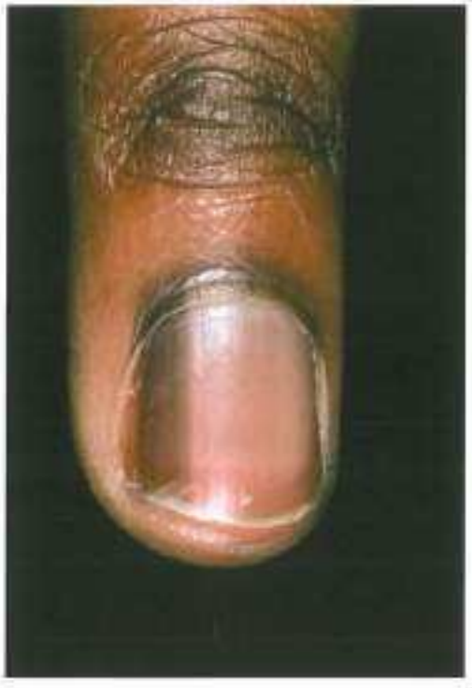


Fig. 25.52 Linear melanonychia. A longitudinal dark band across the nails is a common normal variant in black races. In Caucasians, it may be a sign of Addison's disease.

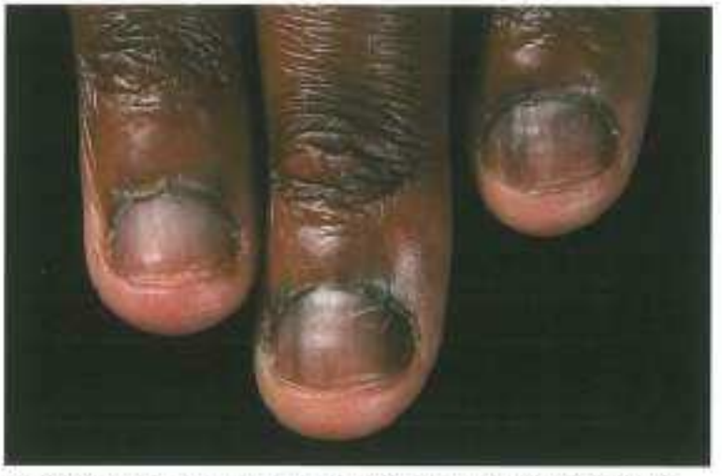


Fig. 25.53 Diffuse melanonychia. The whole nail may be discoloured black. One or several nails may be affected. It is a common normal finding in black-skinned races.

Broad white lines (Fig. 25.50) appear horizontally across the nails secondary to hypoalbuminaemia from whatever cause, particularly cirrhosis and renal disease. They are known as *Beau's nails*. A whiteness of all the nail except the distal edge, which is normal, is known as *Terry's nails*, is associated with cirrhosis, congestive cardiac failure, adult-onset diabetes mellitus, malabsorption and thyrotoxicosis. Vitiligo affecting the distal extremities makes the nailbed appear white, but the surrounding skin is involved (Fig. 25.51).

Dark bands running along the longitudinal axis of the nail plates (Figs 25.52 and 25.53) are very common and are a normal variant in black races, but in Caucasians they may be a sign of Addison's disease or Laugier–Hunziker syndrome. Drugs may also cause longitudinal pigmentation and these include minocycline, zidovudine (in the treatment of HIV infections) and antimalarial drugs. A malignant melanoma may present with a linear pigmented band but it usually has an irregular edge to it.

Koilonychia is a concavity in the nail plate caused by thinning and softening of the nail plate such that it loses its contours and is either flat or spoon-shaped. It is often secondary to iron deficiency anaemia but may occur congenitally (Fig. 25.54) or in association with Raynaud's phenomenon. The nails may become abnormal secondary to infiltration of the underlying skin, for example in amyloidosis (Fig. 25.55; Ch. 22), sarcoidosis (Fig. 25.56) or Sézary syndrome (Fig. 25.57; Ch. 12). In most cases, the skin elsewhere will give the clue to the diagnosis, but amyloid may affect only the nails in which case a biopsy is required to make the diagnosis. Periungual erythema and cuticular haemorrhages are characteristic of lupus erythematosus (Fig. 25.58) and dermatomyositis (Fig. 25.59).

BEAU'S LINES

A horizontal depression occurring across the nail plate of all the nails.

Aetiology

It is caused by interruption in the growth of the nails occurring during a systemic illness, operation or even prolonged labour.

Clinical Features

Symptoms

There is ridging of the nails.

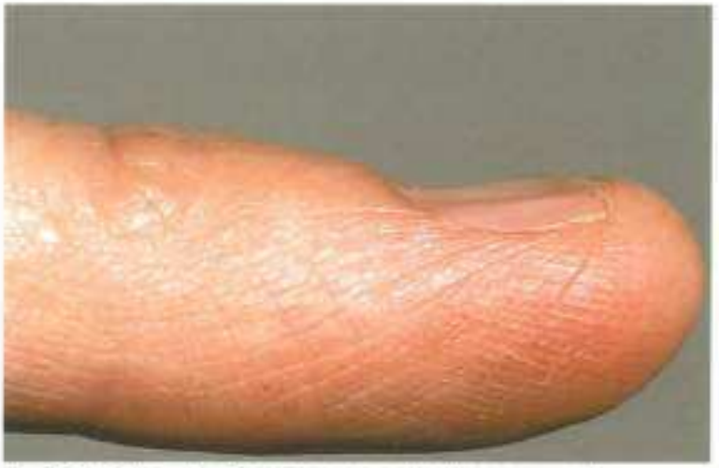


Fig. 25.54 Koilonychia. The nail is concave rather than convex and is thus 'spoon-shaped'. In this case the deformity was congenital. (Courtesy of Dr A. C. Pembroke.)

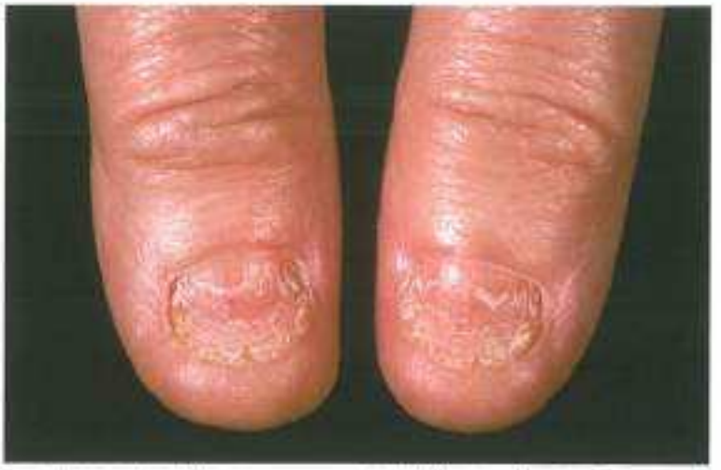


Fig. 25.55 Amyloid. This woman presented with thin atrophic nails. The diagnosis was made by biopsy, which led to the finding of paraproteinaemia.

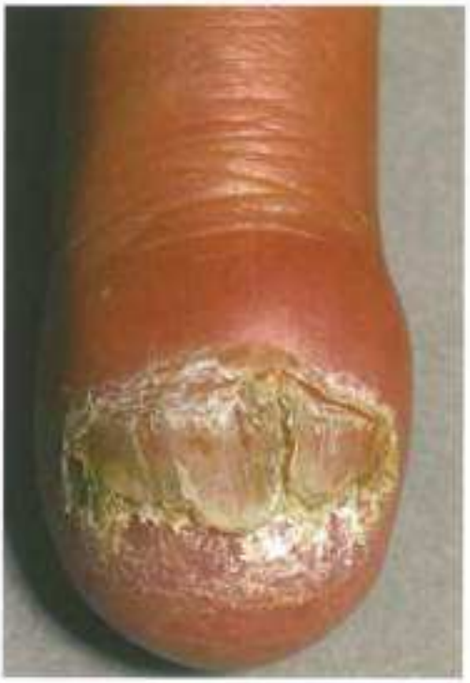


Fig. 25.56 Sarcoidosis. The distal phalanges are expanded with granulomatous tissue and the nails are distorted. Bony cysts can be seen on radiographs.

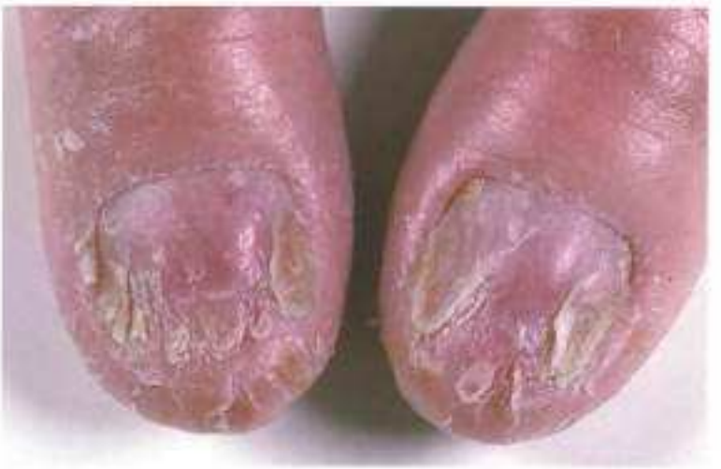


Fig. 25.57 Sézary syndrome. The nailbed is infiltrated by Sézary cells and nail growth is distorted. The patient was erythrodermic.

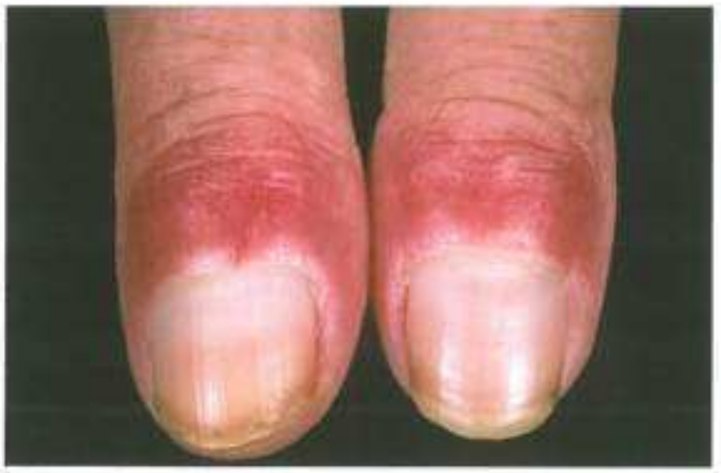


Fig. 25.58 Connective tissue disorders. Periungual erythema occurs in lupus erythematosus, mixed connective tissue disease and dermatomyositis. This patient was HIV positive.

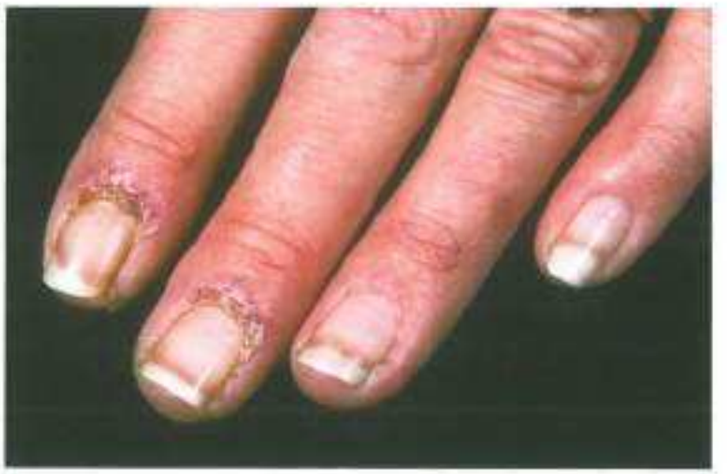


Fig. 25.59 Dermatomyositis. Purple papules over the knuckles with prominent, ragged and haemorrhagic cuticles are characteristic of dermatomyositis.

Fig. 25.60 Beau's lines. Horizontal troughs are noticed midway up the nail about 3 months after an illness.

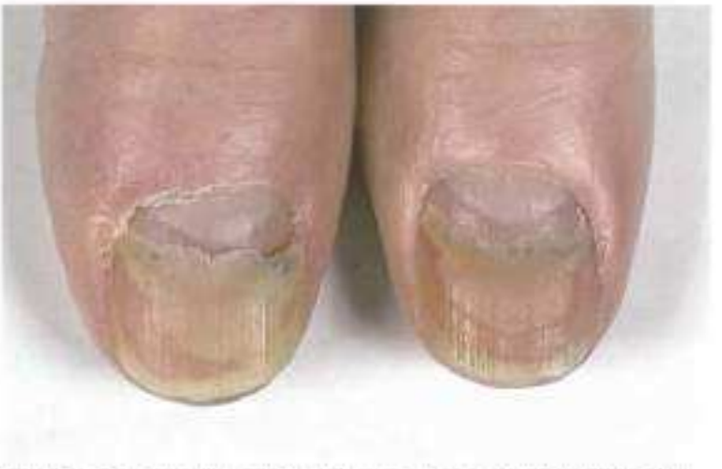


Fig. 25.61 Shedding of the nails. This results from a severe illness, when nail growth is reduced or ceases temporarily.

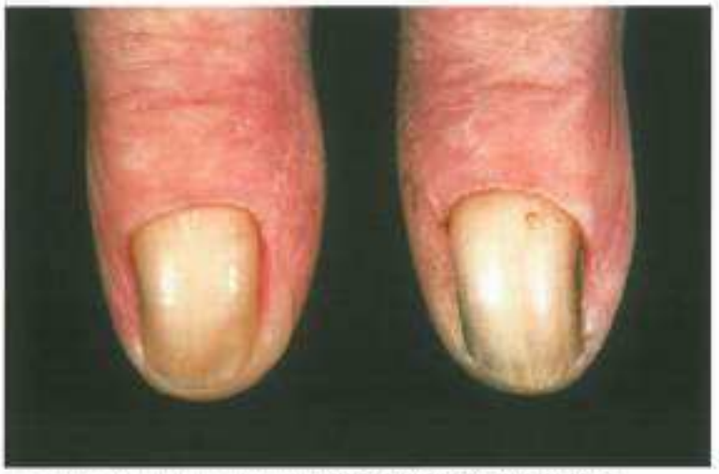


Fig. 25.62 Yellow nail syndrome. The nail is discoloured yellow and is excessively curved, particularly across the horizontal axis.

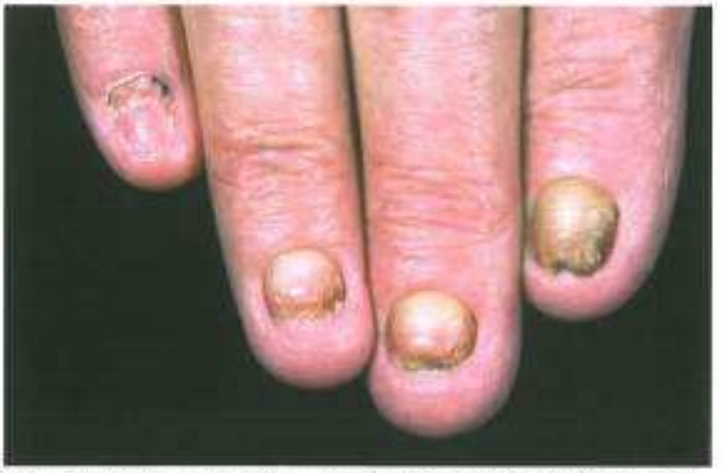


Fig. 25.63 Yellow nail syndrome. All the nails are involved and there is loss of the cuticles. They are thickened, curved and yellow. The syndrome is often associated with pulmonary disorders.

Morphology
A horizontal trough across the nail plate is usually noticed when it is halfway up the nail (Fig. 25.60), which corresponds to 2–3 months of nail growth after the precipitating episode. The degree of change depends on the severity of the illness (Fig. 25.61).

Distribution
All the fingernails and often toenails display the change.

Management
The deformity grows out and the patient can be reassured.

YELLOW NAIL SYNDROME
A rare but distinctive disorder of retarded nail growth associated with lymphatic deficiency and pulmonary abnormalities.

Aetiology
The cause is unknown but the nails fail to grow sufficiently and there is a deficiency of the lymphatics draining the areas. Occasionally lymphoedema is present. There are almost always pulmonary abnormalities, particularly chronic bronchitis, bronchiectasis or even carcinoma of the lung. Sometimes an asymptomatic pleural effusion may be found.

Clinical Features
Symptoms
The nails are discoloured and thickened.

Morphology
The nails are discoloured yellow or yellow-green, thickened and excessively curved (Fig. 25.62), particularly across the horizontal axis. There is loss of the cuticle and a distinctive gap occurs between the skin and the nail, especially along the sides.

Distribution
All the nails are affected (Fig. 25.63).

Management
There is no specific treatment but some remarkable results have been seen in patients treated with vitamin E.

Abnormal circulation and the nails

Specific nail abnormalities are associated with poor peripheral circulation.

Aetiology

Raynaud's phenomenon, peripheral vascular disease and perniosis may produce a thinned nail plate by virtue of the reduction in blood supply.

Clinical Features

Symptoms

Abnormal fingernails.

Morphology

The nails are ridged longitudinally. Splits occur and the nail breaks easily. The nailbed becomes more visible and the nail appears redder than normal. Sometimes onycholysis occurs (Fig. 25.64) and the nail may become secondarily infected with bacteria or occasionally *Candida* sp., resulting in pigmentary changes. Pterygium formation and occasionally permanent nail loss may occur. The peripheries are cool or cold and appear blue.

Distribution

Most of the fingernails.

Management

The cause should be rectified. A vasodilator such as the nicotinic acid derivative inositol nicotinate (Hexopal) and local measures to keep the hands warm, including battery-heated gloves, may help.

Drugs

Drugs may cause:

- Pigmentation. Minocycline (Fig. 25.65), zidovudine (see Fig. 14.87), hydroxyurea (Fig. 25.66) and daunorubicin are common examples.
- Nail growth arrest and haemorrhage. Chemotherapeutic agents are the commonest culprits including methotrexate (Fig. 25.67).

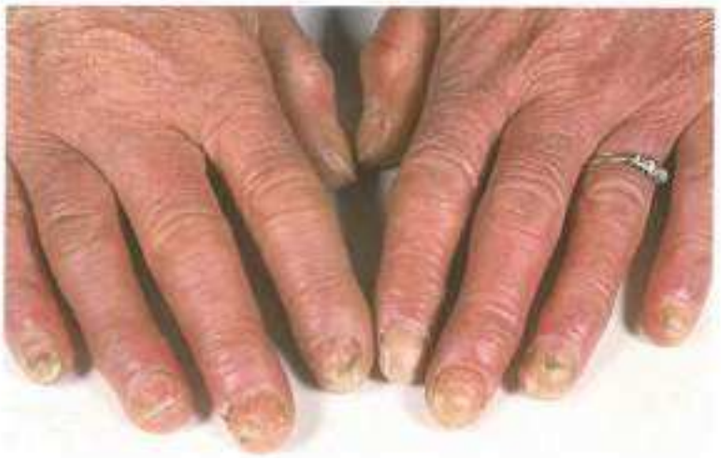


Fig. 25.64 Circulatory disorders. The nail plate becomes thinned if there is poor peripheral circulation. Onycholysis, ridging or splitting of the ends of the nails results. The fingertips are mauve and cold.

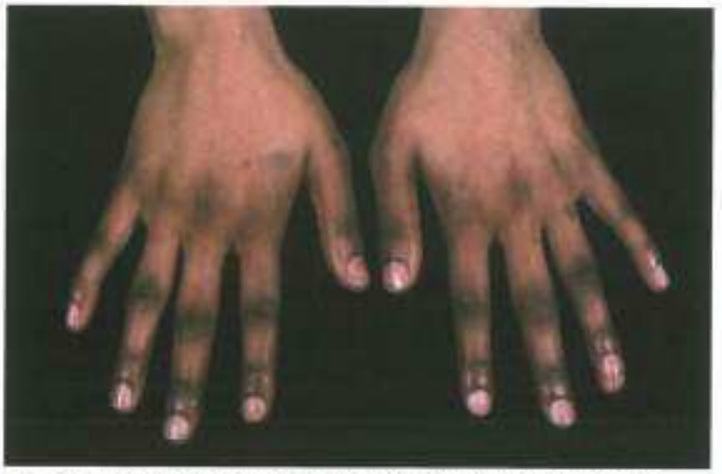


Fig. 25.65 Minocycline pigmentation. All the nails are a bluish colour. The knuckles are hyperpigmented. He had been taking minocycline to treat his acne.

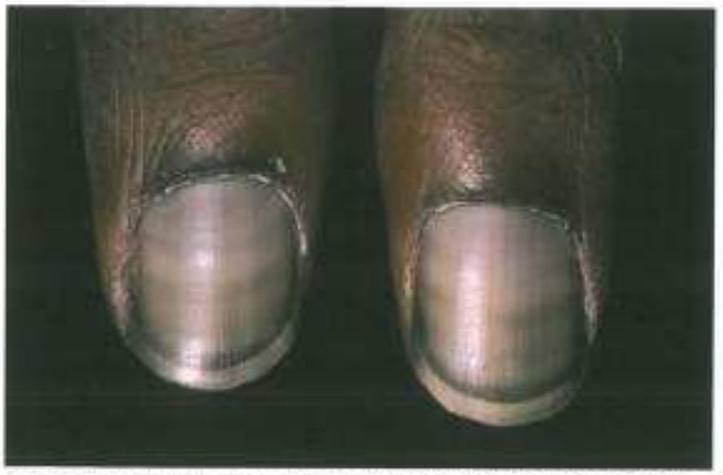


Fig. 25.66 Hydroxyurea pigmentation. The nails are bluish and banded. Other chemotherapeutic agents may produce this sign.

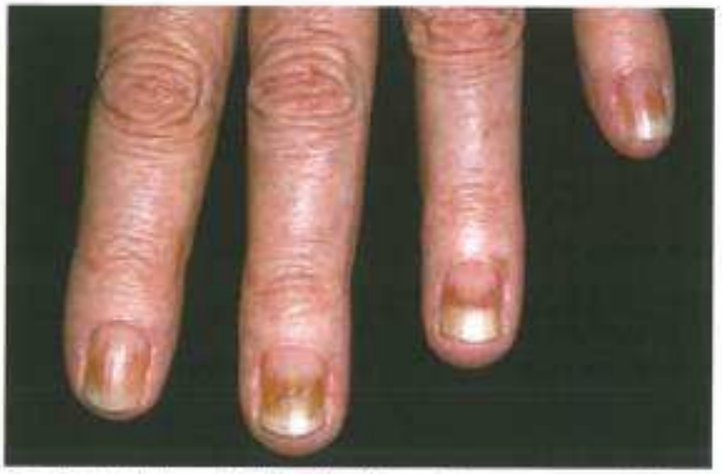


Fig. 25.67 Methotrexate toxicity. Painful haemorrhage may occur under the nail when methotrexate is given in high doses in the management of leukaemia.

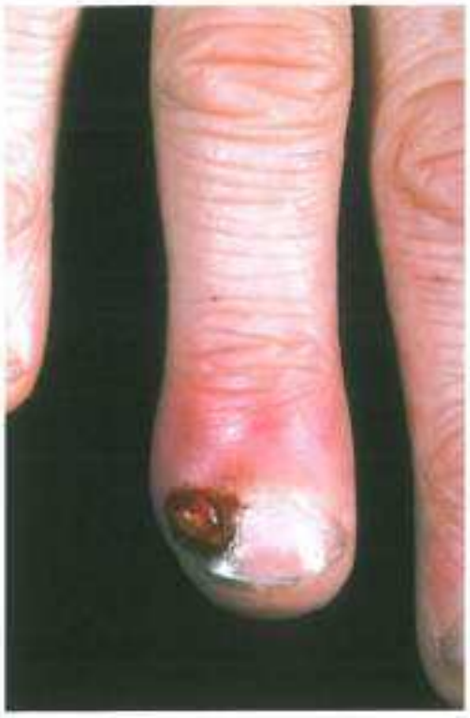


Fig. 25.68 Periungual pyogenic granuloma. Isotretinoin is an occasional cause as are epidermal growth factor inhibitors and antiretrovirals. They may occur spontaneously.

- Periungual pyogenic granulomas (Fig. 25.68). Epidermal growth factor inhibitors, antiretrovirals and isotretinoin are largely responsible.
- Photo-onycholysis (see Fig. 25.46).

Nail trauma

Trauma to the nails is common.

- **Leukonychia** These white spots in the nails (Fig. 25.69) are probably caused by minor trauma, although popular mythology links them to calcium deficiency.
- **Nail biting** Fingernails may be bitten at the tip as far as the point of separation from the nailbed and are irregularly damaged (Fig. 25.70). The cuticles are frequently nibbled as well, which may result in matrix damage. It is a feature of mild anxiety, and other members of the family may be affected. There is no effective treatment although many patients grow out of the habit with time. Warts often accompany nail biting.
- **Habit tic** One or both thumbnails may be damaged by repeated scratching of the nail plate or picking at the cuticle with the fingernail of the index finger of the same hand. A longitudinal depression along the length of the nail is seen, with cross-ridges (Figs 25.71 and 25.72). The habit is difficult to break although fluoxetine has been reported as being effective. Occasionally, patients are deluded (Fig. 25.73). Minor horizontal ridging may result from overzealous pushing back of the cuticles. If the patient desists from the practice, the condition is rectified.

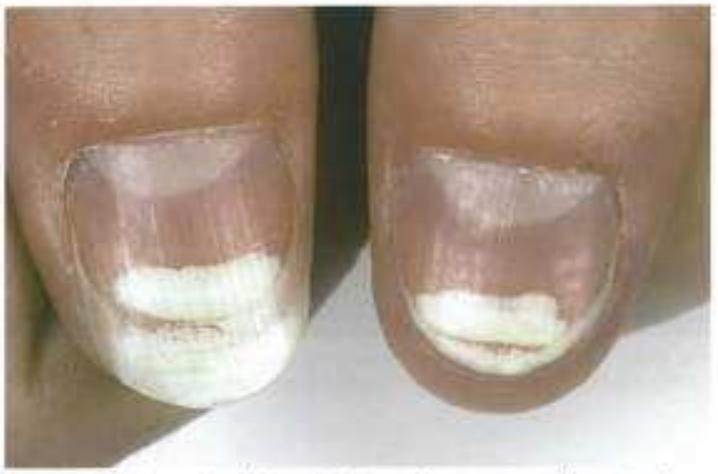


Fig. 25.69 Leukonychia. White spots in the nails are common. More extensive examples may occur. The cause is unknown but trauma may be relevant.

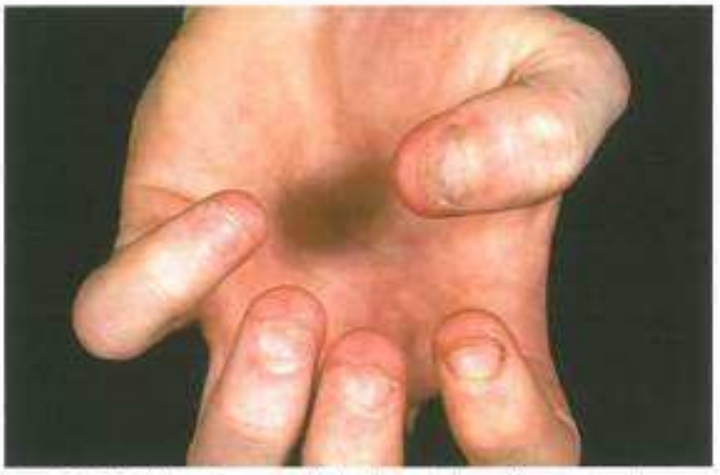


Fig. 25.70 Nail biting. The ends of the nails are broken off to a varying degree. Most improve with time.

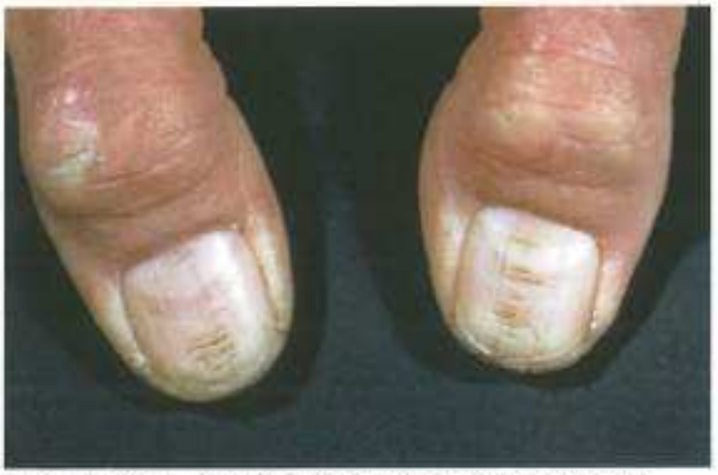


Fig. 25.71 Habit tic. Repeated scratching of the nail plate or picking at the cuticle, produces a longitudinal depression in the nail, with multiple horizontal lines within it. Both thumbnails are affected.

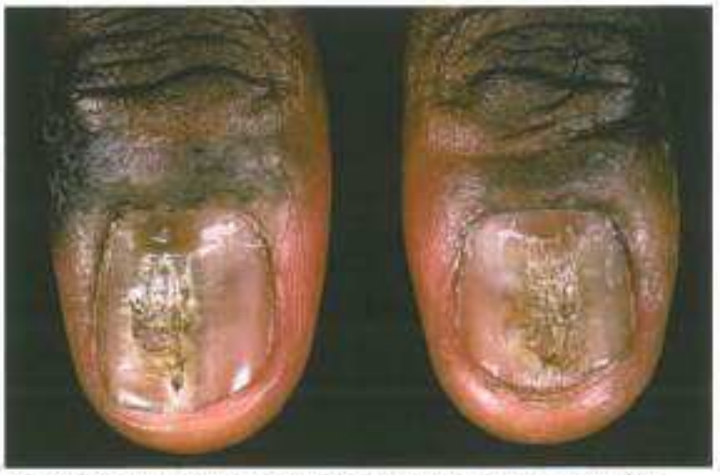


Fig. 25.72 Habit tic. A more severe example is shown. The thumbnails are repeatedly scratched and picked at by the index finger.

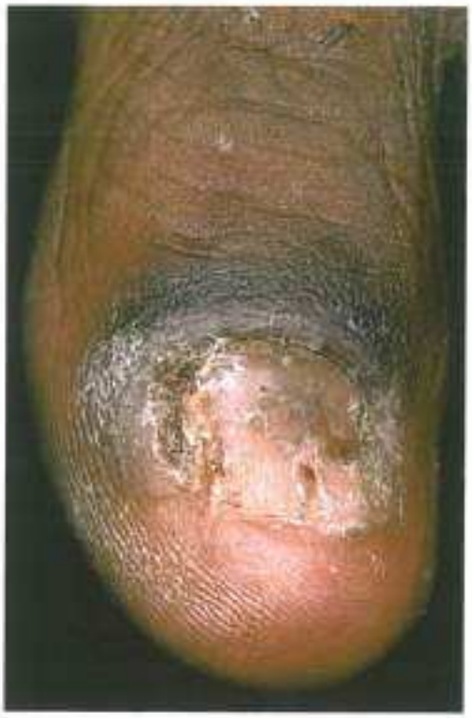


Fig. 25.73 Delusional parasitophobia. This patient was convinced that his skin and nails were infested. He continually tried to gouge 'worms' out of his nails.

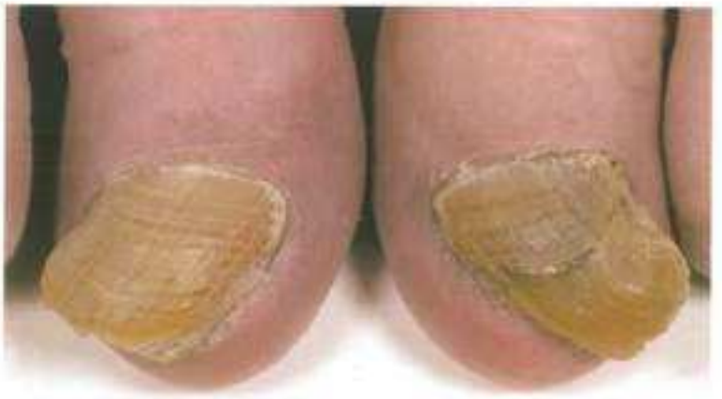
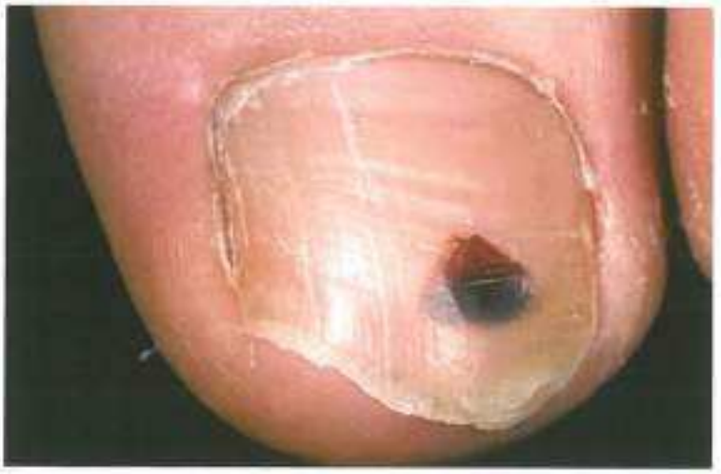
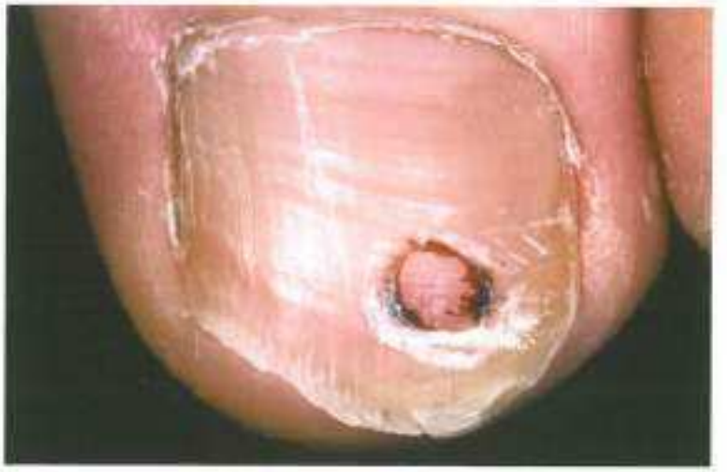


Fig. 25.74 Onychogryphosis. Chronic trivial trauma ultimately interferes with nail growth on the big toes. The nails grow outwards and are thickened and discoloured.





Figs 25.75 and 25.76 Haematoma. The normal nail (Fig. 25.76) may be revealed by cutting away the haemorrhage within the nail with a scalpel.

- **Physical injury** The big toenail is most vulnerable because it is prominent and frequently injured (the injury is often trivial and forgotten, e.g. kicking a football, stubbing the toe) or chronically traumatized by wearing shoes that are high-heeled, pointed, open-toed or ill fitting, particularly during childhood as the feet are growing. This minor trauma ultimately leads to abnormal growth of the nail. The commonest abnormalities that result are:
  - **Dystrophic nails** The nail becomes discoloured and thickened and often grows out laterally. In more severe cases, the nail becomes grossly thickened, discoloured, excessively curved, hard and elongated (Fig. 25.74), ultimately simulating a ram's horn (*onychogryphosis*). It was originally known as the ostler's nail, as it was usually seen in grooms whose toes were frequently trampled on by horses. Dystrophic nails are often mistaken for a fungal disorder and treated as such, but it is always wiser to take clippings for mycology before embarking on treatment. In a young healthy individual, it is reasonable to advise radical removal of the nail and its matrix. In the elderly, frequent chiropody is the best approach.
  - **Haematoma** A red, brown or purple lesion is seen under the nail, often with pin-point haemorrhage. The discoloration will move up the nail as it grows. The old blood may be removed with a scalpel (Figs 25.75 and 25.76).

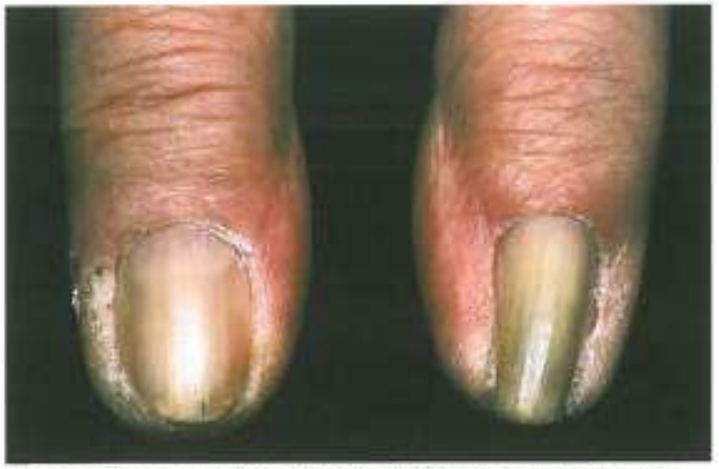


Fig. 25.77 Pincer nails. Overcurvature of the fingernails is usually congenital. Overcurvature of the toenails (especially the nail of the big toe) is usually caused by poor-fitting footwear.

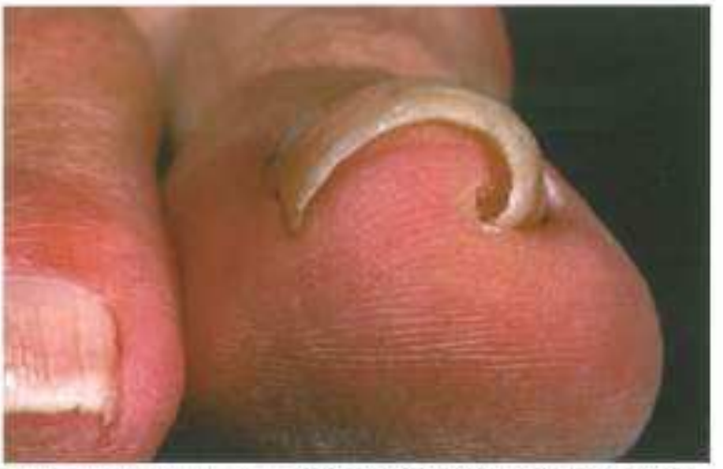
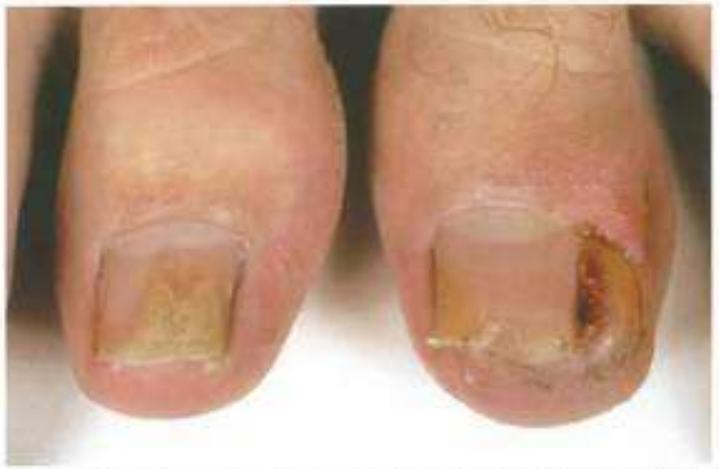
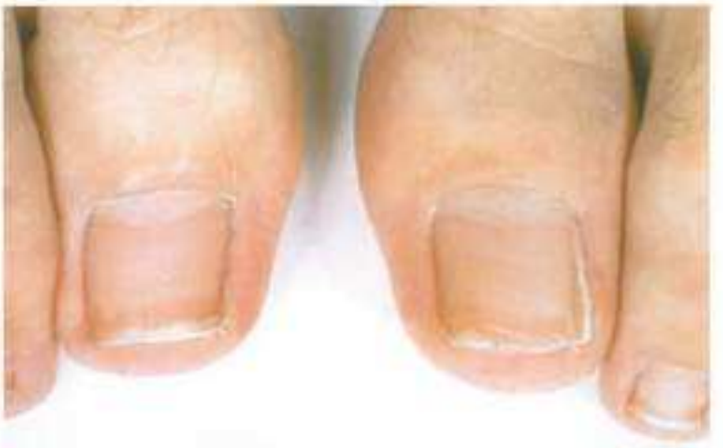


Fig. 25.78 Ingrowing toenail. The toenail is incurving and growing into the toe.





Figs 25.79 and 25.80 Ingrowing toenail. Heaped-up granulation tissue occurs at the side of the big toe. Ill-fitting shoes, which give rise to chronic trauma, are the commonest cause. This man also had tinea unguium and the condition responded to surgery and griseofulvin (Fig. 25.80).

- **Overcurvature of the nails (pincer nail deformity)** There may be discomfort if the curvature is such that the edges cut into the lateral nailfolds. It is usually caused by ill-fitting footwear but may be congenital. The large toenails are predominantly affected but others may be (Fig. 25.77). Chiropody is required for pincer nails, but permanent avulsion may be necessary for the congenital varieties.
- **Ingrowing toenails** Discomfort and inflammation occur secondary to ingrowing of the toenail (Fig. 25.78). Granulation tissue may result from small projections of the nail, which cut into the lateral nailfolds (Figs 25.79 and 25.80) and sometimes detach and act as a foreign body. An ingrowing toenail usually results from ill-fitting footwear coupled with cutting the nail in a half-circle instead of straight across, which permits the nail to penetrate into the skin. Sometimes it results from a chronic tinea infection, which so distorts the nailbed that the nail grows abnormally into the skin. Rectification of these factors, use of potassium permanganate soaks as an antiseptic and insertion of a cottonwool plug under the edge of the nail to allow it to grow out straight are helpful measures. Granulation tissue should be destroyed by cautery. If this fails, the nailfold should be excised under a digital nerve block. Sometimes the nail has to be avulsed.

LAMELLAR NAIL DYSTROPHY

A splitting of the nail plate into its component layers secondary to repeated wetting and drying out of the nails following frequent immersion in water. (Also known as onychoschizia).

Aetiology

The condition is most common in women. It may occur in men but they rarely present for diagnosis. The normal nail consists of several layers of keratin. Frequent immersion of the hands and fingernails in water may soften the nail and the consequent drying damages the cells of the nail plate such that they do not adhere together properly. This permits the nail plate to separate into its component layers and these tend to split off distally.

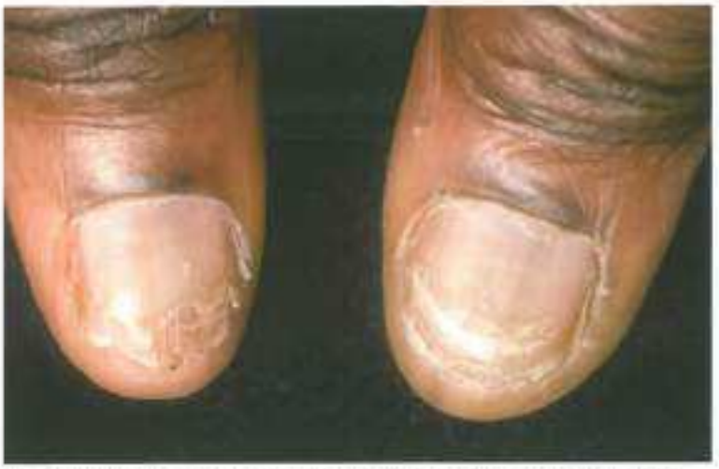


Fig. 25.81 Lamellar nail dystrophy. Frequent immersion in water causes the nail plate to separate into component layers, which tend to split off distally.

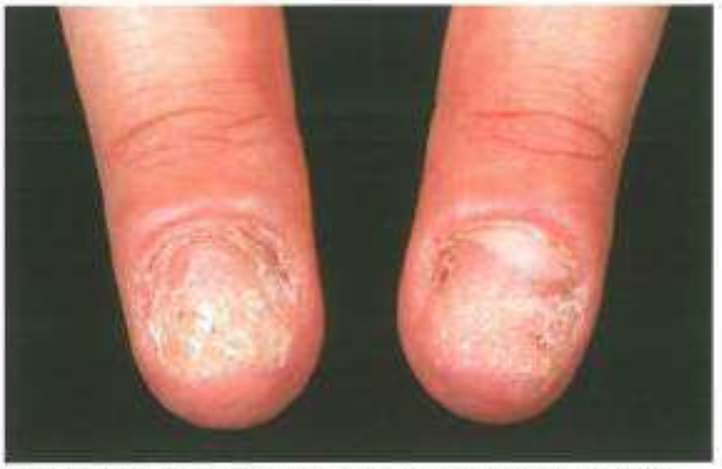


Fig. 25.82 Contact dermatitis caused by acrylic. Contact dermatitis may occur secondary to acrylate in false nails. Here there is dystrophy and loss of the nails. Variable amounts of damage result.

Clinical Features

Symptoms

There is splitting of the nails.

Morphology

The distal ends of the nails split into layers (Fig. 25.81).

Distribution

The fingernails are affected.

Management

Explanation and advice on reducing exposure to water coupled with protective measures is all that is required.

NAIL COSMETIC DYSTROPHY

Nail cosmetic dystrophy is nail abnormality caused either by direct trauma to the nail or by a contact allergy.

Aetiology

Stick-on nail dressings and artificial fingernails may cause nail dystrophies. These materials are not porous and prevent the normal free exchange of moisture between the nail and the atmosphere. When the dressings of nails are taken off, portions of the nail plate are pulled away with the adhesive. This produces an irregular surface and splits the nail into layers. Leuconychia and onycholysis may result.

Artificial fingernails may also be made by mixing a liquid monomer and powder acrylic polymer together on the nail. These are then shaped to improve the appearance of the nail. Acrylic is a potent contact sensitizer of the skin and if the patient does sensitize to it, onycholysis and sepsis may occur. Formalin is incorporated into nail hardeners and may also cause onycholysis. Other chemicals, including phenol, are also added from time to time to nail cosmetics, and occasionally epidemics of onycholysis and other nail disorders may occur.

Clinical Features

Symptoms

The nails have an abnormal appearance.

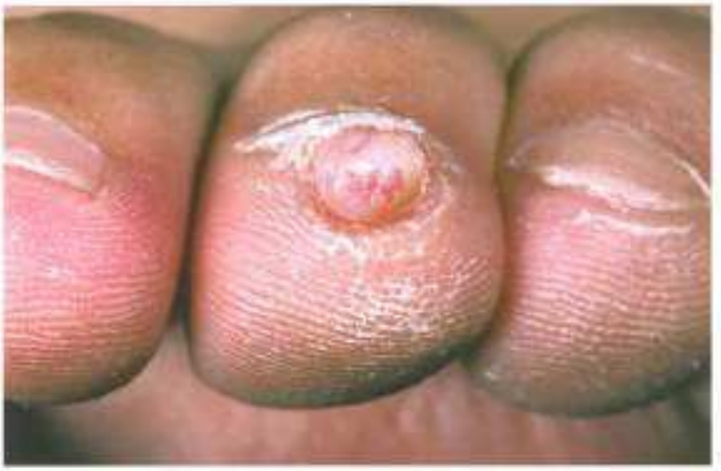


Fig. 25.83 Subungual exostosis. There is a nodule under the distal aspect of the nail, causing it to be elevated.

Morphology

Separation of the nail from the nailbed is the most common abnormality, but ridging and sepsis of the nail, which cause marked nail dystrophy (Fig. 25.82), are common.

Management

Contact dermatitis may be proven by patch tests to acrylic. The patients will recover in most cases if they desist from using the materials.

Conditions surrounding the nails

Many of these conditions are described elsewhere but they include inflammatory and infiltrative disorders such as eczema, psoriasis, lichen planus, connective tissue diseases, sarcoidosis and cutaneous T cell lymphoma. Benign tumours include subungual exostosis (Figs 25.83,

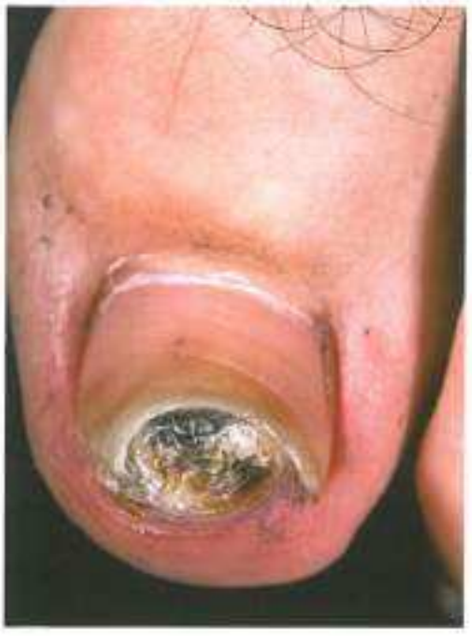


Fig. 25.84 Subungual exostosis. Commonly mistaken for a wart, it occurs beneath the big toe particularly. It represents a bony outgrowth.

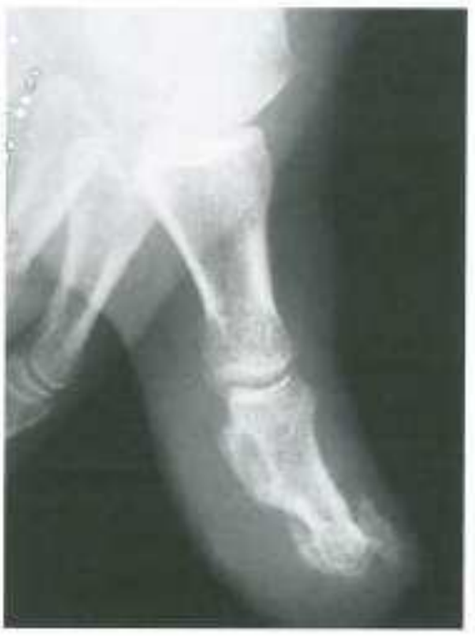


Fig. 25.85 Subungual exostosis. Calcification can be seen under the thumbnail on this radiograph.

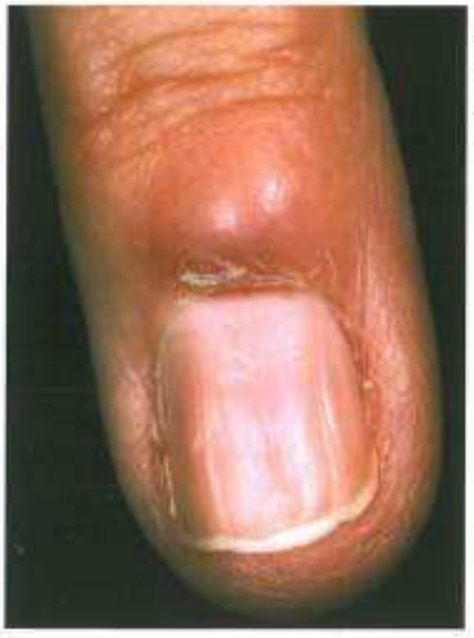


Fig. 25.86 Myxoid cyst. There is a smooth, well-circumscribed, firm, flesh-coloured nodule overlying the distal interphalangeal joint.

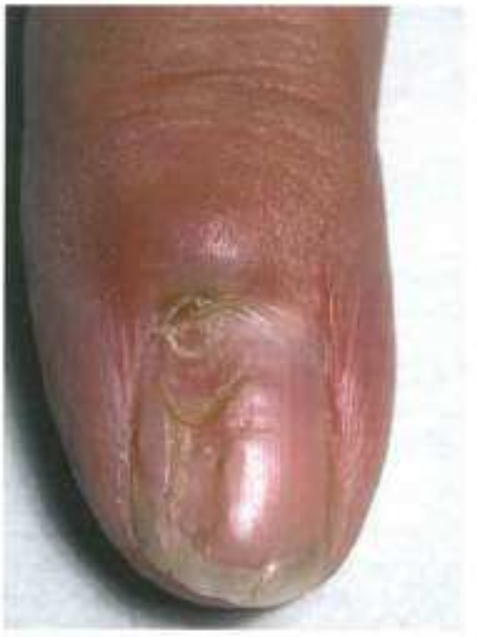


Fig. 25.87 Myxoid cyst. The swelling overlying the nail matrix results in a longitudinal furrow. It may be excised but frequently recurs. It sometimes responds to intralesional triamcinolone.

25.84 and 25.85), implantation epidermoid cysts, pyogenic granuloma, glomus tumours (see Fig. 9.152), myxoid cysts [Figs 25.86–25.88], periungual fibromas of Koenen (associated with tuberous sclerosis) (Fig. 25.89), acquired periungual or digital fibrokeratomas (Fig. 25.90), accessory digits (Fig. 25.91), enchondromas (often as part of Maffucci's syndrome) and viral warts (Fig 25.92). Malignant tumours encompass Bowen's disease (Fig. 25.93), squamous cell carcinoma [Figs 25.94 and

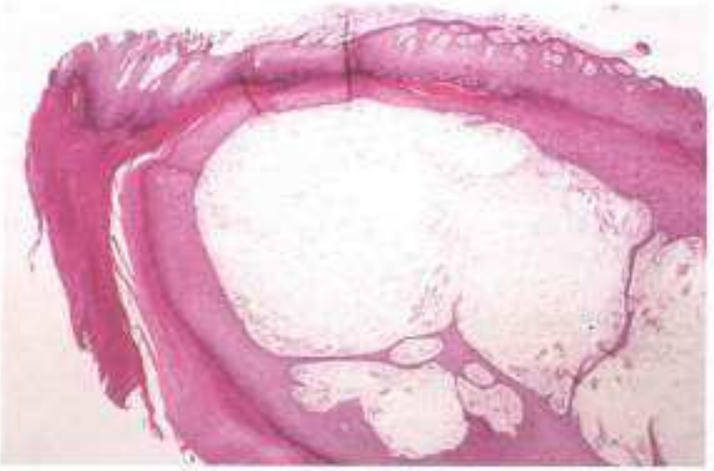


Fig. 25.88 Myxoid cyst. The dermis is expanded and largely replaced by abundant pale staining myxoid tissue with irregular stellate fibroblasts, giving rise to a multiloculated 'cystic' lesion.

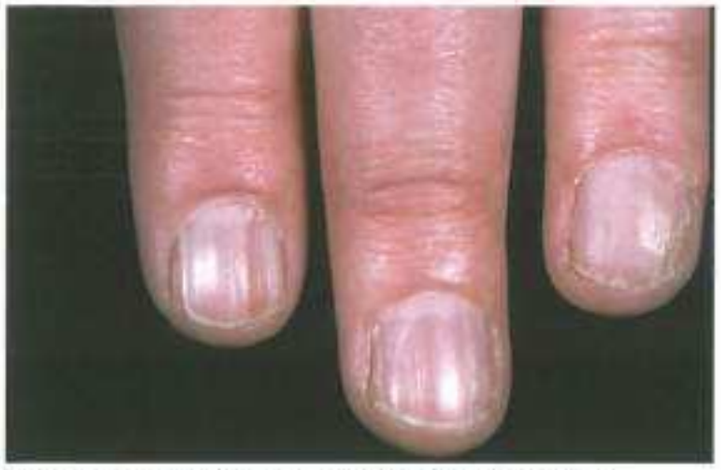


Fig. 25.89 Tuberous sclerosis. The periungual fibromas cause linear depressions in the nails.

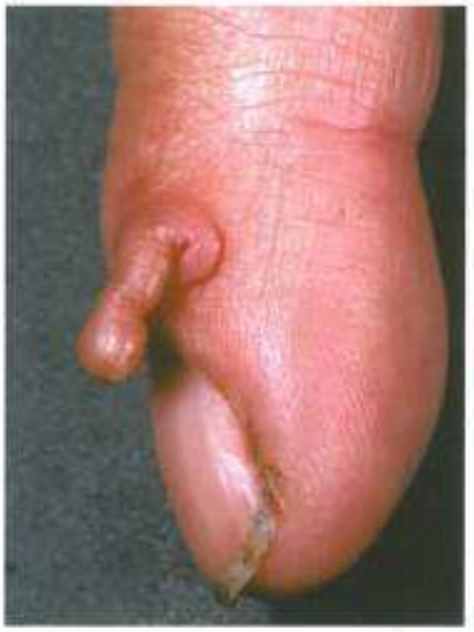


Fig. 25.90 Periungual digital fibrokeratoma. The lesion is most common in adult males and probably results from trauma.

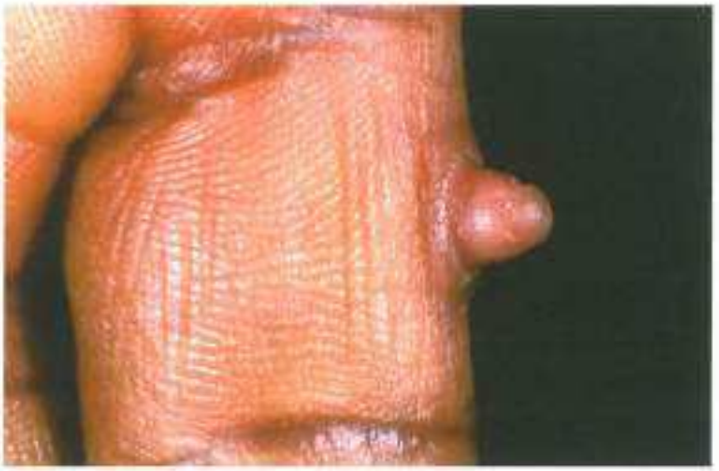


Fig. 25.91 Accessory digit. This is present at birth which distinguishes it from a digital fibrokeratoma (Fig. 25.90).

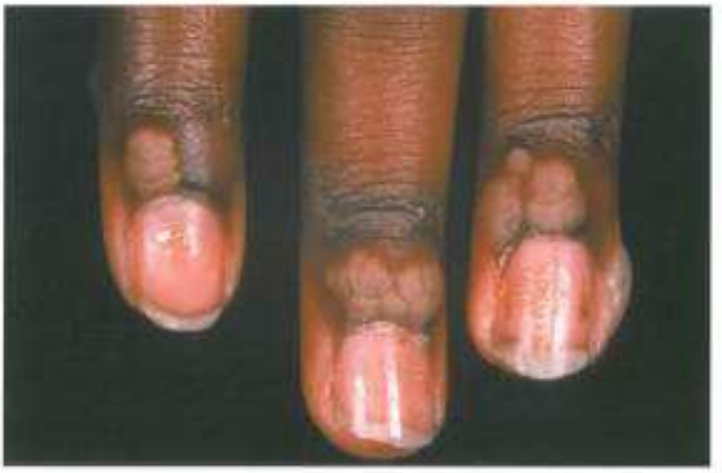


Fig. 25.92 Viral warts. Periungual warts are common, but particularly resistant to treatment requiring multiple and frequent applications of liquid nitrogen.

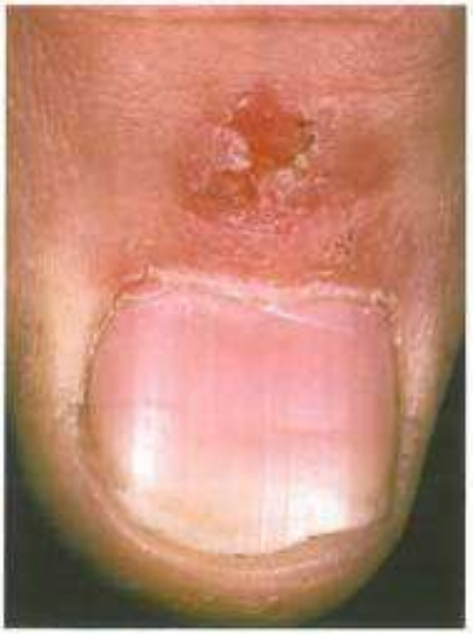


Fig. 25.93 Bowen's disease. This well-defined red raw plaque (biopsy-proven intraepidermal carcinoma) responded to topical 5-fluorouracil but recurred. It was subsequently treated successfully with photodynamic therapy.

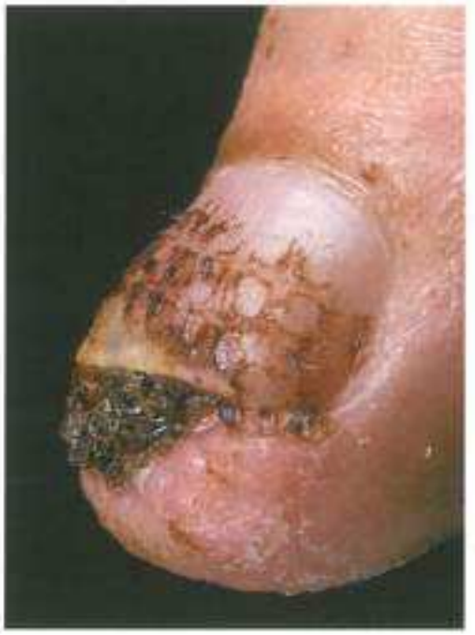


Fig. 25.94 Squamous cell carcinoma under the nail. There is a hyperkeratotic lesion under the nail, which has bled. A biopsy is indicated to establish the nature of the lesion; in this case a squamous cell carcinoma.

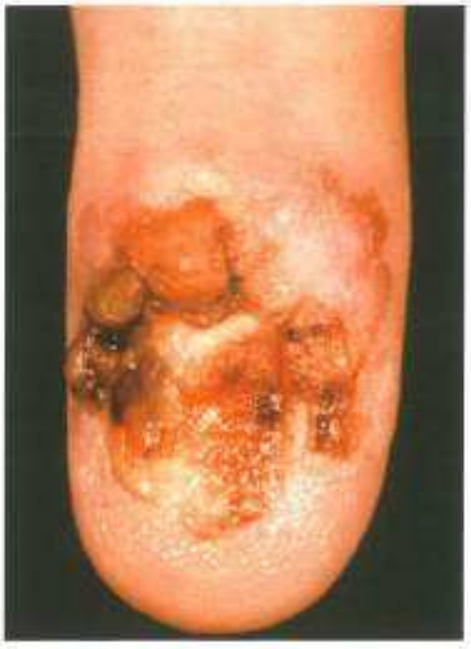


Fig. 25.95 Squamous cell carcinoma of the nail. There is destruction of the nail by a hyperkeratotic tumour, which has haemorrhaged.

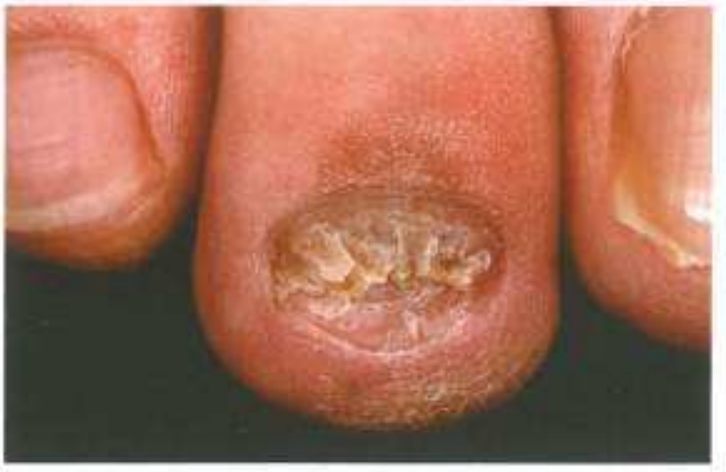


Fig. 25.96 Malignant melanoma of the nailbed. The nail was growing abnormally and has become thickened. There is pigmentation under the nails and around the posterior nailfold (Hutchinson's sign).

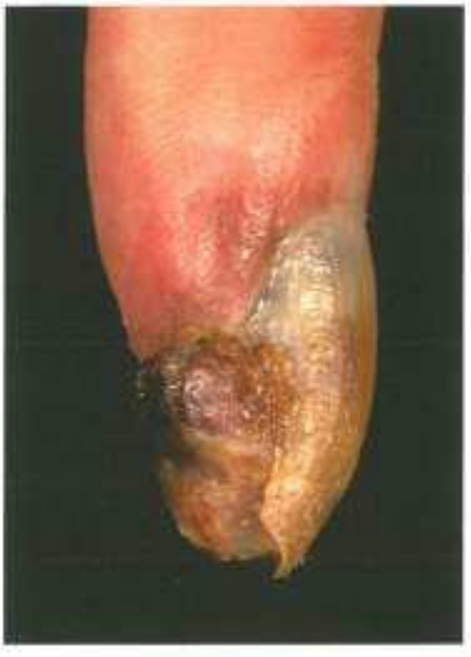


Fig. 25.97 Malignant melanoma. There is pigmentation of the nailfold and a friable tumour under the nail causing pigmentation and dystrophy of the nail plate. Biopsy is required to establish the diagnosis.

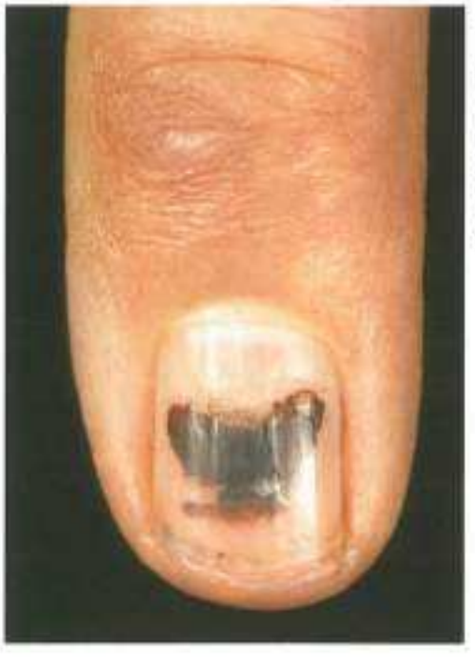


Fig. 25.98 Trauma. The colour may be black generally but there is usually a red-brown or russet discoloration as well as pinpoint dots of haemorrhage. The configuration may be quite straight as it grows out.

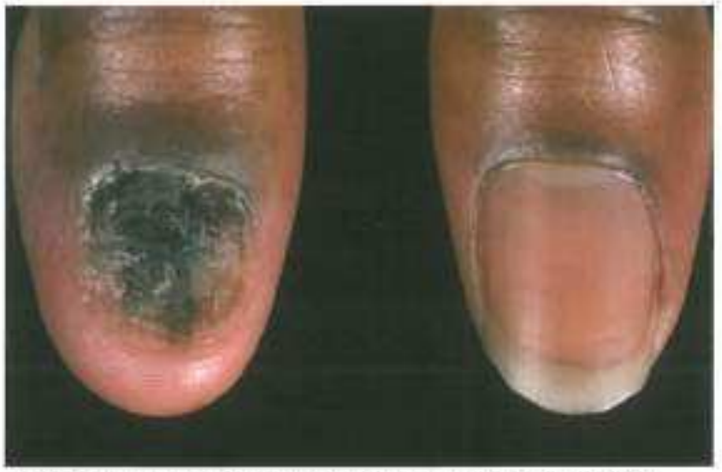


Fig. 25.99 Tinea. Fungal hyphae are found on direct microscopy of the nail. Culture grew *Trichophyton soudanense*.

25.95), malignant melanoma (Figs 25.96 and 25.97; see Figs. 11.72–11.74) and metastases, usually from a carcinoma of the bronchus.

The differential diagnosis of malignant melanoma and black discoloration under the nail include *Pseudomonas* infection (see Fig. 25.22), trauma (Fig. 25.98), linear melanonychia (see Figs 25.52 and 25.53), tinea (Fig. 25.99) and candida (see Fig. 25.6).

Congenital disorders of the nails

Congenital disorders of the nails are extremely rare and range from micronychia (Fig. 25.100), complete absence of the nails from birth, or malalignment (Fig. 25.101) to supernumerary digits and nails. Often a family history of such abnormalities is present. Changes may be seen as a result of a generalized disorder of the skin, such as *epidermolysis bullosa*, where the nails are destroyed secondary to peri- and subungual blistering (Fig. 25.102) results in onycholysis, nail thickening and shortening and

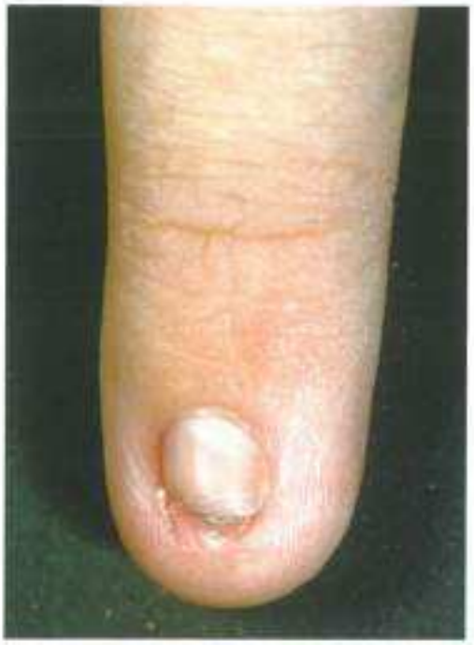


Fig. 25.100 Micronychia. Nails may be partially or totally absent, as the result of a congenital defect. (Courtesy of Dr A. C. Pembroke.)

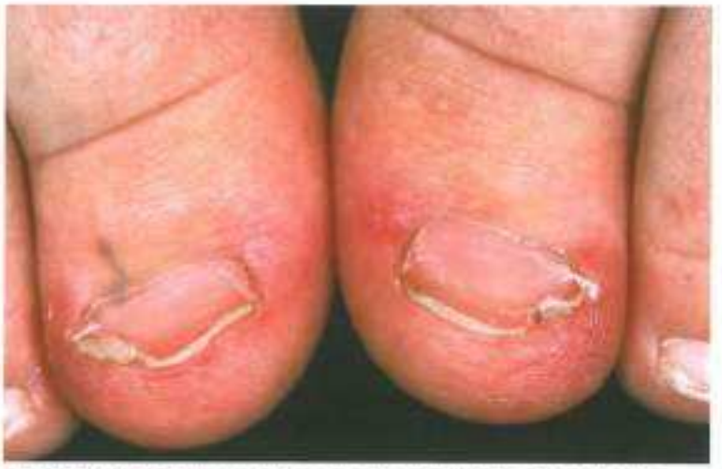


Fig. 25.101 Malalignment of the nails. There is lateral deviation of the big toenails from birth. It usually results in ingrowing toenails.

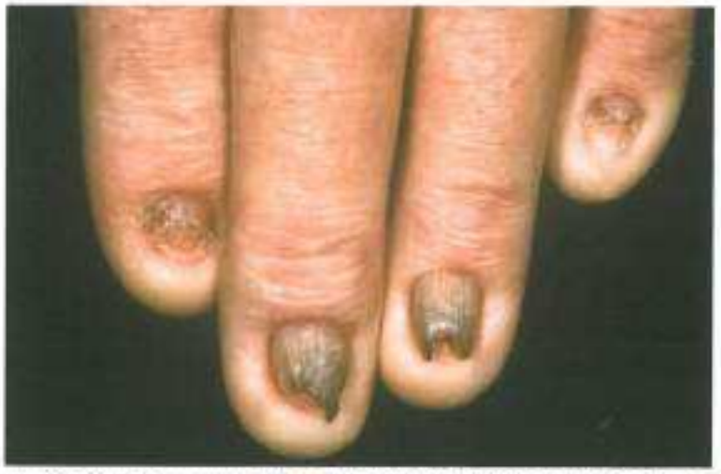


Fig. 25.102 Epidermolysis bullosa. The diagnosis of these dystrophic nails was missed for 72 years until Dr Jemima Mellerio, having noted the milia and scarring on the patient's knees and elbows, confirmed it by electron microscopy.

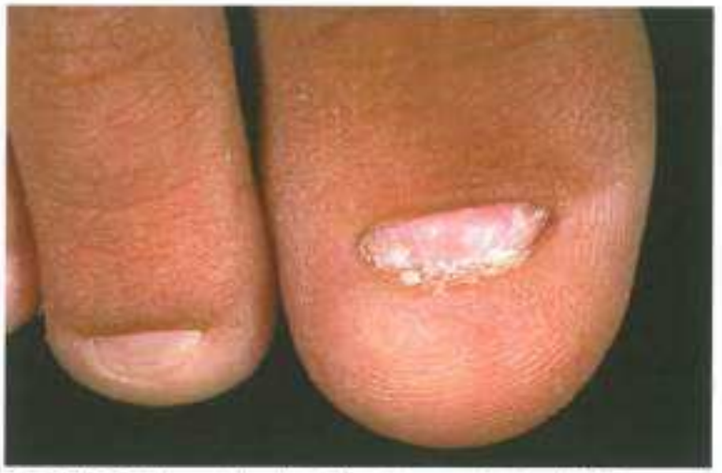


Fig. 25.103 Ectodermal dysplasia. The nails were rudimentary in this 3-year-old child with ectodermal dysplasia.

also pterygium formation and nail atrophy. It may be the first or only symptom in some families with dominant dystrophic or epidermolytic epidermolysis bullosa, or late onset junctional epidermolysis bullosa. Alternatively, the nails may be involved as part of a generalized ectodermal disorder where the nail changes are really of secondary importance, for example *ectodermal dysplasia* (Fig. 25.103) or *Darier's disease* (Fig. 25.104), tuberous sclerosis (Fig. 20.107), dyskeratosis congenita (Fig. 20.130) and focal dermal dysplasia (Figs 20.136 and 20.137).

MEDIAN NAIL DYSTROPHY

A condition usually of the thumbnail of unknown aetiology where there is a longitudinal split in the nail, starting at the cuticle (*Dystrophia unguis mediana canaliformis*).

Clinical Features

Symptoms

The thumbnail is deformed.

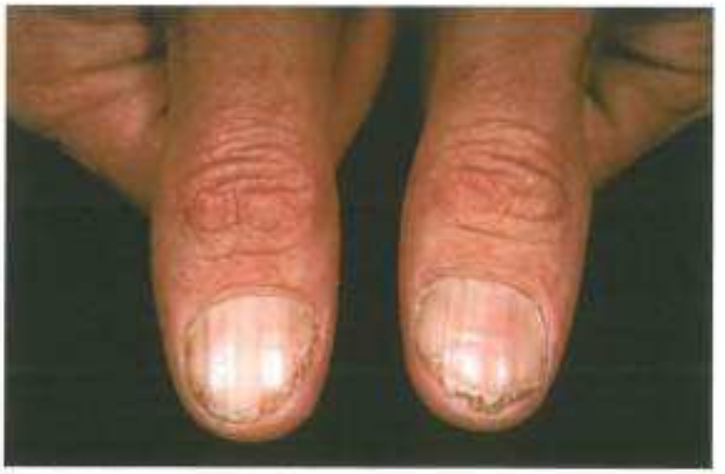


Fig. 25.104 Darier's disease. Splits and notches occur in the distal edges of the nails. There may also be red or white longitudinal streaks.

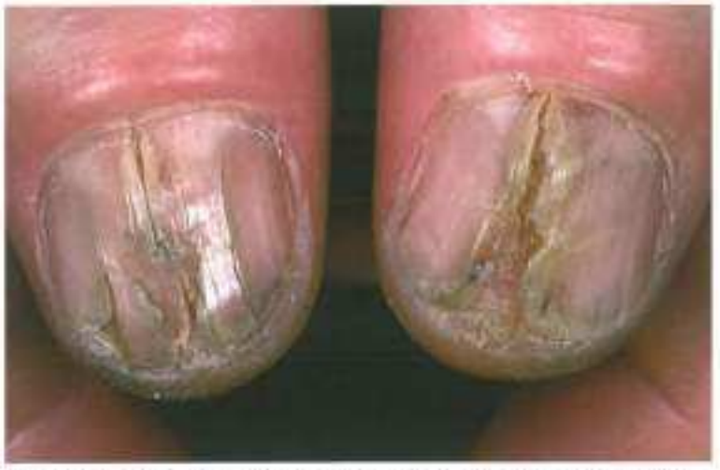


Fig. 25.105 Median canaliform nail dystrophy. A split starts at the cuticle and develops longitudinaly along the nail.

Fig. 25.106 Median nail dystrophy. A longitudinal split is present and in appearance may be likened to an inverted fir tree. The thumbnails are most often involved. (Courtesy of Dr M. Clement.)

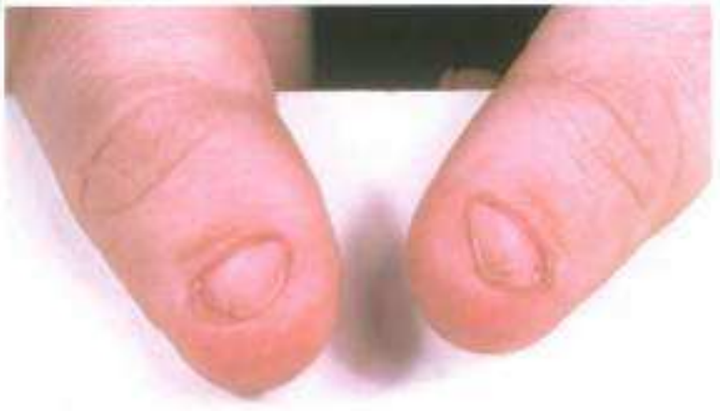


Fig. 25.107 Nail patella syndrome. The thumbnails are either absent or partially formed, particularly on the radial side. Other nails may be involved to a lesser extent.

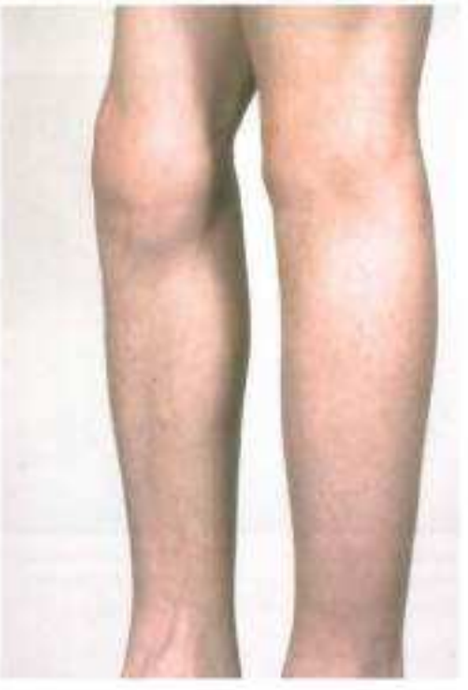


Fig. 25.108 Nail patella syndrome. The patellae are either rudimentary or absent.

Morphology

A split begins at the cuticle and develops in a longitudinal manner along the nail (Fig. 25.105). Splits also occur off the main one, giving an appearance resembling the branches of a fir tree (Fig. 25.106). The lunula is enlarged.

Management

The condition does recover and grows out with the nail, but relapses are frequent. The cause is quite unknown, but because the lunula is often much larger than normal, the matrix may be more vulnerable to trauma.

NAIL PATELLA SYNDROME

An autosomal dominant osteo-onychodysplasia.

Aetiology

There is a mutation in the LMX 1B gene, which encodes a transcription factor which regulates collagen synthesis. Mutations result in ectodermal and mesodermal abnormalities. In addition to the nail and bone abnormalities there may be hyperextensibility of the joints, skin laxity, hyperhidrosis and renal abnormality.

Clinical Features

Symptoms

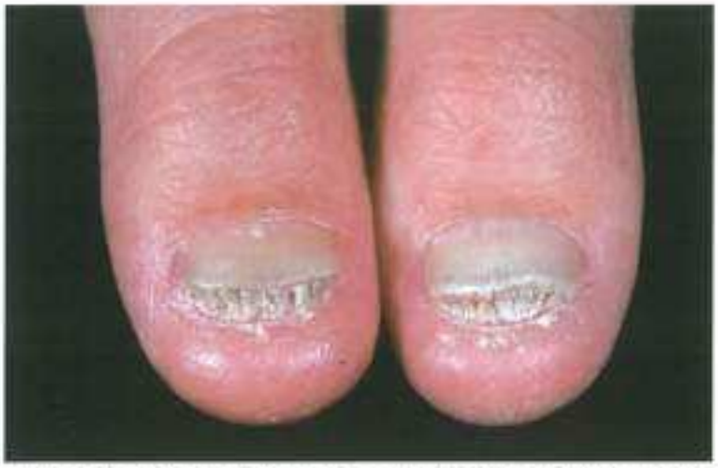
The thumbnails are always involved and often the rest of the nails, but not to such a great degree. Picking up small objects may be difficult.

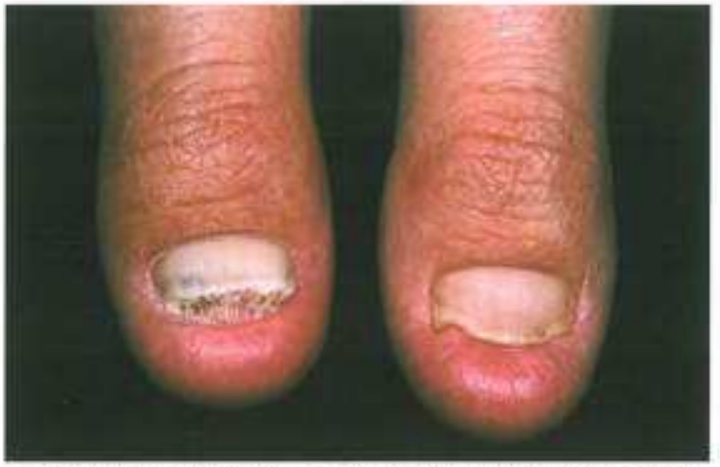
Morphology

A triangular lunula is virtually diagnostic. The nails may be absent, fragile, grooved, hypoplastic, ridged longitudinally with splitting, and rough.

Distribution

The thumbnails are always involved (Fig. 25.107) with the other nails often being involved to a lesser degree and in a decreasing manner towards the fifth nail.





Figs 25.109 and 25.110 Pachyonychia congenita. Within the first year the nails become thickened, especialy at the tip, and wedge-shaped. The thumbs are affected more than the fingers. Laser treatment may be helpful (Fig. 25.110).

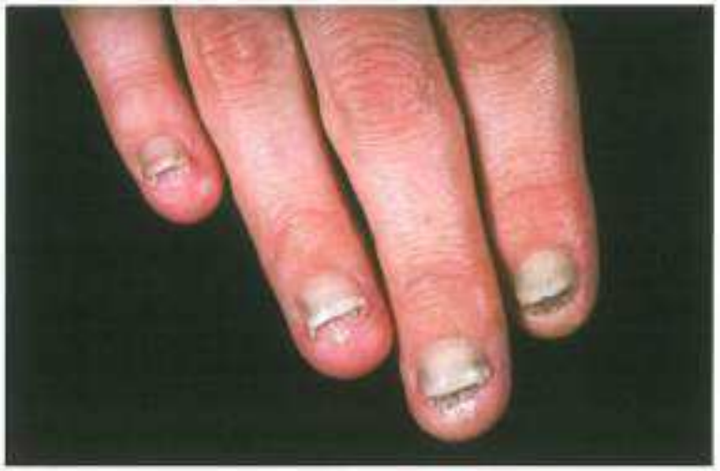


Fig. 25.111 Pachyonychia congenita. There is a gradation of involvement of the nails from the thumb to the little finger.

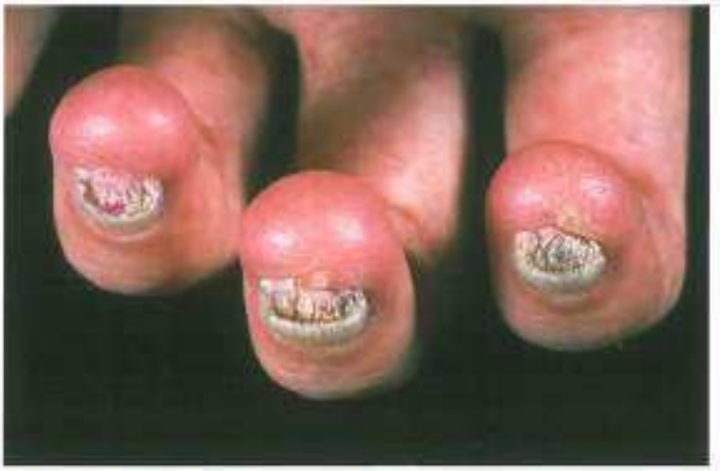


Fig. 25.112 Pachyonychia congenita. The nails are discoloured and thickened particularly distally and may result in onycholysis.

Systemic features

The patella are either rudimentary or absent (Fig. 25.108). There is radial head dysplasia and iliac crest exostoses. 40% have nephropathy, which may result in renal failure.

Management

There is no treatment at present.

PACHYONYCHIA CONGENITA

An autosomal dominant condition of grossly thickened nails and hyperkeratosis, particularly of the soles of the feet, associated sometimes with other abnormalities.

Aetiology

There are essentially two types. Type I of Jadassohn–Lewendowsky (PC-I) is associated with mutations of the genes for keratin 6A and 16, and type II (Jackson–Lawler type) is with mutations of keratin 6B and 17 expression. Keratins 16 and 17 are expressed in differentiated epithelial structures, such as nailbed, mucosa and palmoplantar epidermis. PC-1 comprises hypertrophic nail dystrophy, painful diffuse or focal symmetrical hyperkeratosis of palms and soles especially at friction or pressure points or over weight-bearing areas. Sometimes there are erosions and follicular hyperkeratosis of the extensor surfaces and leucokeratosis of the tongue and oral mucosa and occasionally there is laryngeal involvement giving rise to hoarseness. In PC-II, the plantar changes may be minor but there are multiple epidermal cysts, steatocystomas or eruptive hair cysts at puberty. All have woolly hair and eyebrows that grow straight outwards. They may have neonatal teeth.

Clinical Features

Symptoms

The nails are usually normal at birth but within the first year they become abnormal, with the thumbnail (Figs 25.109 and 25.110) being more affected than the others (Fig. 25.111). Keratoderma of the soles is usually present by 7 years of age. The palms may only be affected in manual workers.

Morphology

The nails are discoloured and thickened, which is more pronounced at the tip than at the base (Fig. 25.112), giving a wedge-shaped appearance. It is more obvious on the fingernails than on the toenails.

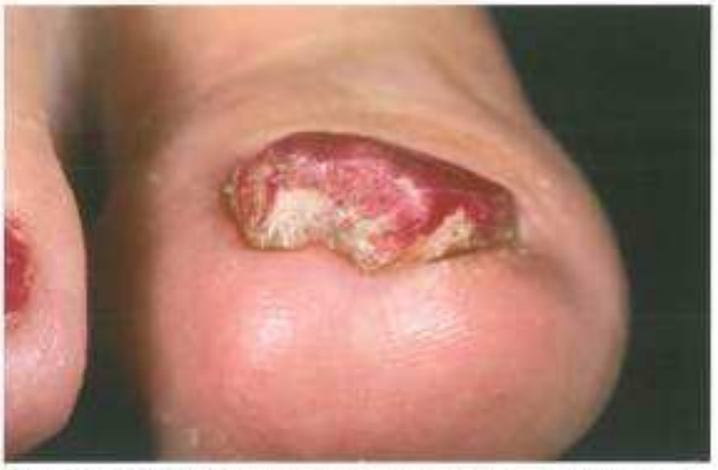


Fig. 25.113 Pachyonychia congenita. Within the first year, the nails become thickened, particularly at the tip, and wedge shaped.

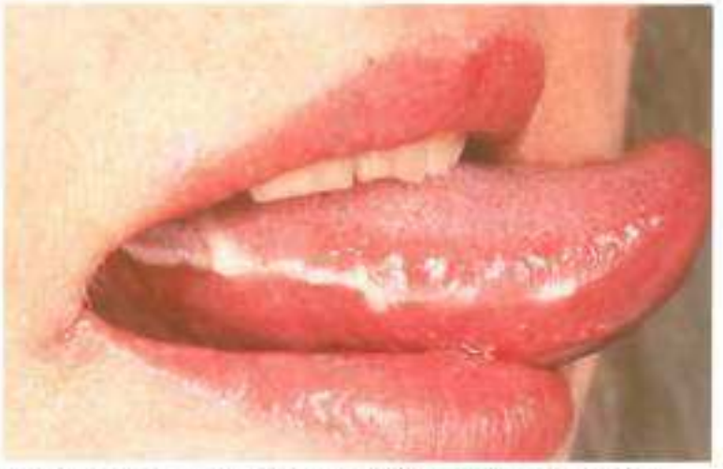


Fig. 25.114 Pachyonychia congenita. There is a whiteness and thickening (leukokeratosis) along the sides of the tongue in type I disease.

Distribution
In addition to the nail dystrophy (Fig. 25.113), leukokeratosis of the tongue (Fig. 25.114) and hyperkeratosis of the hands and feet (Fig. 25.115) may be present. The latter is complicated by blistering, particularly in the summer.

Distribution
The nails and the weight-bearing skin of the feet are affected.

Management
Good chiropody and sensible shoes may help any discomfort, but acitretin and laser ablation of the hyponychium may be helpful in some cases.

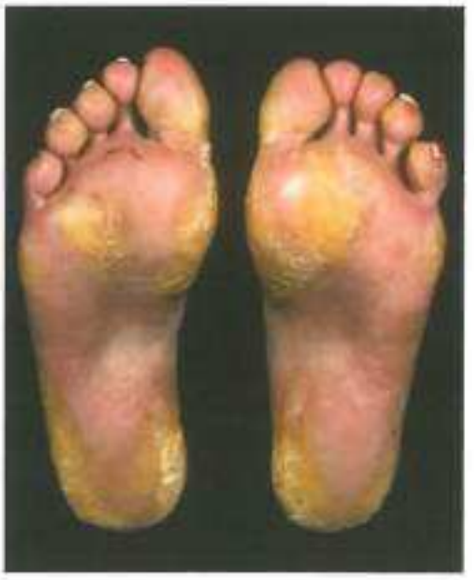


Fig. 25.115 Pachyonychia congenita. There is symmetrical hyperkeratosis of the soles, which is more pronounced on weight-bearing areas. The palms may also be involved.

NAIL EN RAQUETTE
An autosomal dominant inherited disorder of unknown aetiology, which results in failure of development of the distal phalanx of the thumb.

Clinical Features
Symptoms
There is an abnormal thumbnail.

Morphology and distribution
The distal phalanx of the thumb is shorter and wider than normal (Fig. 25.116) and consequently the nail is affected. There are no related abnormalities.

Management
There is no necessity for treatment.

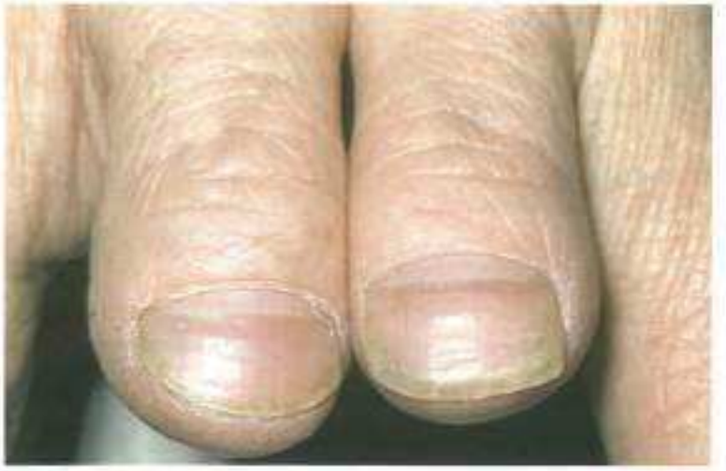


Fig. 25.116 Nail en raquette. The distal phalanx of the thumb fails to develop fully, so it is shorter and wider than normal, as is the nail.

Disorders of the hair and scalp

26

The structure and function of hair are described in detail in Chapter 2. Essentially it is composed of keratin, which is a protein made by mitotically active cells at the base of the hair follicle. The follicle is an invagination of the epidermis and the bulb at its base encloses a highly vascular area of dermis. Any influence that interferes with mitosis or compromises the blood supply will affect the hair.

The hair shaft consists of several layers. The principal one is the cortex, which in terminal hair has a central medulla. Surrounding the cortex is a cuticle and an outer and inner root sheath. Structural abnormalities, either genetically determined or induced by trauma, may occur and result in increased fragility of the hair shaft and shortened hair. Since the hair is keratinous, it may also be invaded by fungi.

There are three types of hair: Lanugo hair is present in utero and shed during the eighth month and is only visible in premature babies (Fig. 26.1). It is soft, fine, unmedullated and usually unpigmented. Very rarely, lanugo hair is not replaced after birth and persists indefinitely. Acquired *hypertrichosis lanuginosa* is exceptionally rare but has been associated with malignant disease, particularly of the gastrointestinal tract, bronchus and breast.

Vellous hair is the fine, downy hair that covers the skin other than the palms, soles and parts of the genitalia. It may be transformed into terminal hair by androgens.

Terminal hair is thicker and more pigmented than vellous hair. It comprises the medullated hair of the scalp, eyebrows and eyelashes and at puberty develops in the axillae and pubic area of both sexes and, in the male, also in the beard area and body. It may also occur in these areas in the female, when it is known as *hirsutism* (Fig. 26.2), which may or may not be part of a more general disorder known as *virilism*.

Hypertrichosis, in contrast, is used to describe growth of terminal hair in an area that is not normally hairy. It can occur in a localized manner, such as in naevi (melanocytic, Becker's and fauntail, or generalized as in anorexia nervosa, porphyria (Fig. 26.3), epidermolysis bullosa, Hurler's

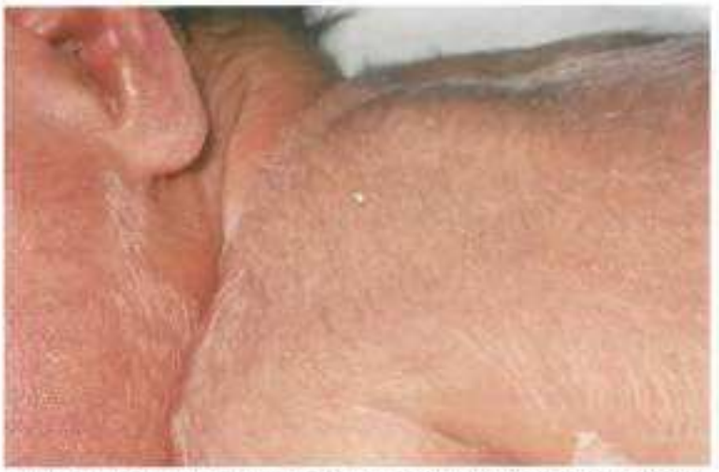


Fig. 26.1 Hypertrichosis lanuginosa. This child was delivered at 32 weeks and the soft, fine unmedullated, unpigmented lanugo hair is still present. It is usually shed at 8 months of gestation.

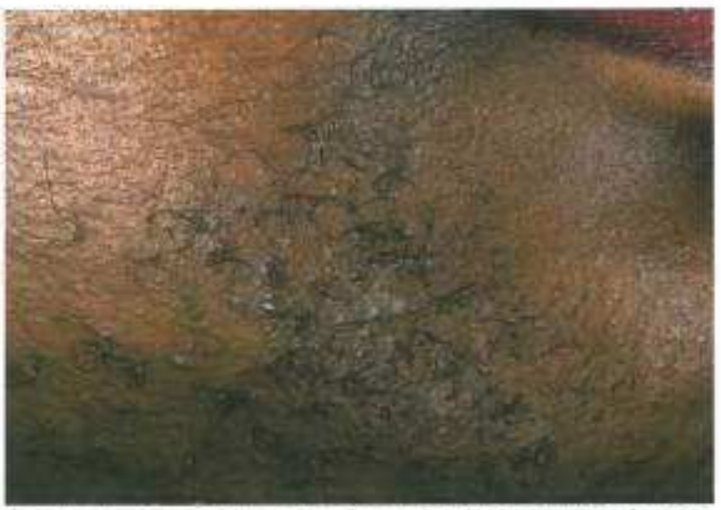


Fig. 26.2 Hirsutism. This is growth of coarse terminal hairs in females in normally non-hairy sites. It is frequently a racial characteristic.

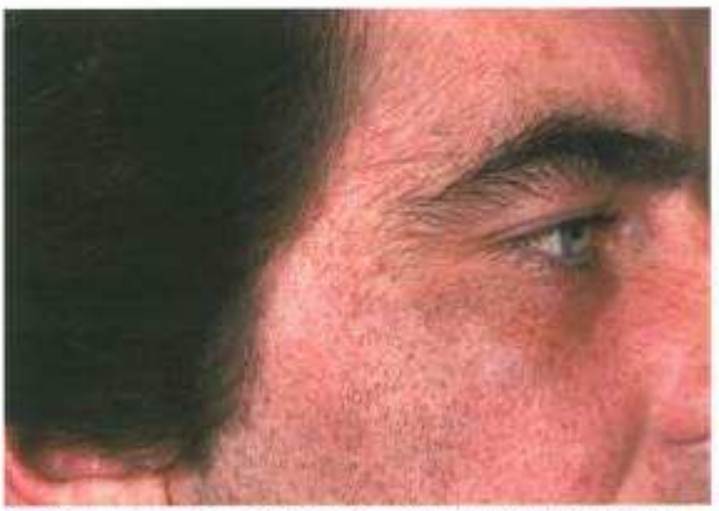


Fig. 26.3 Hypertrichosis. This means the growth of terminal hair in a normally hairless area; in this patient with porphyria, growth occurred between the eyebrow and scalp.

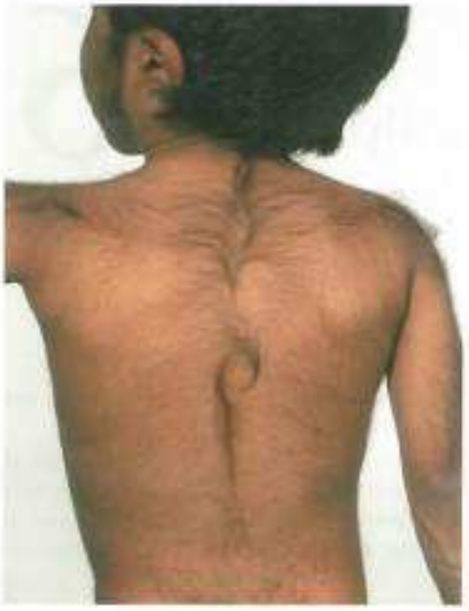


Fig. 26.4 Hypertrichosis. This child has Noonan's syndrome and was being treated with ciclosporin, which causes hypertrichosis.

Fig. 26.5 Male escutcheon in a female. The growth of pubic hair towards the umbilicus is under the influence of testosterone only and is, therefore, absent in most females. In pathological hirsutism, there is android obesity (an increase in the waist-to-hip ratio).

syndrome and Cornelia de Lange syndrome. Certain drugs, such as corticosteroids, diazoxide, ciclosporin (Fig. 26.4) and penicillamine may be responsible.

Hair colour depends on what type of melanin is formed. Thus eumelanin is present in brown or black hair, and phaeomelanin (a product of dopaquinone and cysteine) in blonde or red hair. As the amount of melanin in the hair shaft decreases with age, greying (*canities*) occurs. This may occur prematurely and is an inherited predisposition. Greying also occurs in pernicious anaemia and thyroiditis. In certain forms of albinism and phenylketonuria, the hair is white or blonde. In copper deficiency, as in *Menkes' kinky hair syndrome*, the hair colour is light because copper is required by tyrosinase for the production of melanin. Severe protein malnutrition and iron deficiency also lighten hair. Silvery hair may be a pathological feature of a *Chédiak–Higashi syndrome*, which is associated with oculocutaneous hypopigmentation and defective chemotaxis of neutrophils, infections and lymphoid malignancy.

Hormonal Influences on Hair Growth

Secondary sexual hair growth results from the change of vellous to terminal hair. This is under the direct control of androgens at puberty. Pubic and axillary hairs develop first, followed by facial and body hair. Androgens are secreted as testosterone by the Leydig cells of the testis in the male and as weak androgenic steroids, androstenedione and dehydroxyepiandrosterone, by the ovaries in females and by the adrenals in both sexes. Pubic and axillary hair are extremely sensitive to these androgens and are maximally developed in both sexes. The upper triangle of pubic hair, which grows towards the umbilicus, is under the control of testosterone alone, which explains why males have hair in this area and females usually do not. It is known as the male escutcheon (Fig. 26.5). The lower triangle of pubic hair is under the control of both adrenal and testicular androgens.

Testosterone is a powerful androgen and, after the completion of puberty, males are maximally virilized by it; consequently, no further hair growth can occur in the male, even in the presence of an adrenal tumour that secretes androgen. Therefore, virilization is a term that is only applicable to a prepubertal child (Fig. 26.6) or a female. The physical signs of virilization are:

- Thickened coarse skin
- Enlarged pores, oiliness and acne
- Temporal recession and male-pattern thinning
- Hirsutism
- Clitoromegaly
- Hypertrophy of the penis and increased folding of scrotal skin in boys
- Hyperpigmentation of sexual zones in children
- Male musculature
- Accelerated growth of long bones and premature closure of epiphyses
- Loss of subcutaneous fat around shoulders and girdle
- Deepening of the voice
- Oligo- or amenorrhoea and infertility.

The causes are:

- Increased production of ovarian androgens secondary to polycystic ovaries or an ovarian tumour

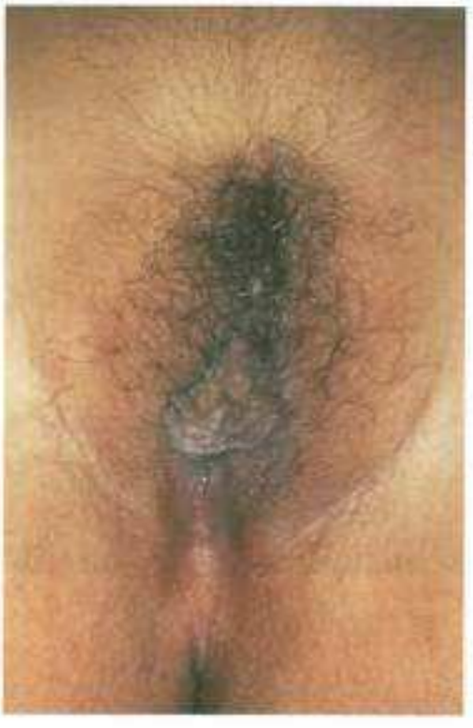


Fig. 26.6 Precocious puberty. This 2-year-old girl is virilized. There is clitoromegaly and hirsutism. (Courtesy of Dr C. Buchanan.)

Fig. 26.7 Hypopituitarism. Hypopituitarism results in adrenal and testicular failure and, as a result, secondary sexual hair growth fails.

- Increased production of adrenal androgens secondary to an adrenal tumour or hyperplasia, or hyperpituitarism, Cushing's disease or prolactin-secreting adenomas
- Defects in steroid metabolism as part of the adrenogenital syndrome
- Ovarian failure either postmenopausal or postoophorectomy
- Androgenic drugs, for example testosterone, danazol, systemic steroids
- Ectopic ACTH production by lung (especially small cell) carcinoma or a carcinoid tumour
- Ectopic gonadotropin production by a choriocarcinoma.

Hormonal causes of decreased hair growth include adrenal failure and hypopituitarism (Fig. 26.7). The former is more evident in females because in males testicular androgen metabolism is not impaired. In hypopituitarism, axillary hair growth diminishes first, followed by pubic and then beard growth, which results in a decreased need to shave. There may be thinning of scalp hair. The skin is also thin and fine, with decreased sebum, sweat and pigment production.

Constitutional hirsutism

The growth of terminal hair on areas of the body unwanted by the patient, usually female.

Aetiology

Hirsutism is the excess growth of terminal hairs in females in a male-like distribution (Fig. 26.8) either due to androgen excess (secreted by the ovaries or adrenal glands), increased end-organ sensitivity or as an idiopathic (constitutional) phenomenon, where there is normal ovulatory function and circulating androgen levels.

Ovarian and adrenal hyperandrogenaemia is associated with a diminished biological response to insulin (insulin resistance). Pseudoacanthosis nigricans (Fig. 26.9) is often present. The commonest cause is obesity. Insulin resistance does occur in non-obese patients, but they have an increased hip-to-waist ratio, which is known as android obesity. It is a common problem and may be measured clinically using the Ferriman and Galway scale as modified by Abraham. Nine areas of the body (upper lip, jaw, sternum, upper and lower abdomen, arms, inner thighs, upper back and lumbar-sacral region) are graded on a 1–4 basis and added together. Less than 8 is regarded as normal. Greater than 25 is viewed as highly suspicious of a systemic cause.

In constitutional (or dermatological) hirsutism, there may be a slight but not significant increase in adrenal androgens (persistent adrenarche syndrome), ovarian androgens (excess ovarian androgen release syndrome) or prolactin. These are known as SAHA (seborrhoea, acne, hirsutism and alopecia) syndromes. They do have recognizable clinical features. In the *persistent adrenarche syndrome* they are usually stressed young women with menstrual cycles longer than 30 days, significant seborrhoea and acne, central hirsutism and sometimes androgenetic alopecia. In the *excess ovarian androgen release syndrome*, the women are in late adolescence, have pronounced seborrhoea, papulopustular acne, mild lateral facial and mammary hirsutism, androgenetic alopecia, shortened or normal periods and obesity. In the *hyperprolactinaemic SAHA syndrome*, the hirsutism is central and lateral with oligomenorrhoea and sometimes acne, seborrhoea and galactorrhoea. The HAIR-AN syndrome is described later.

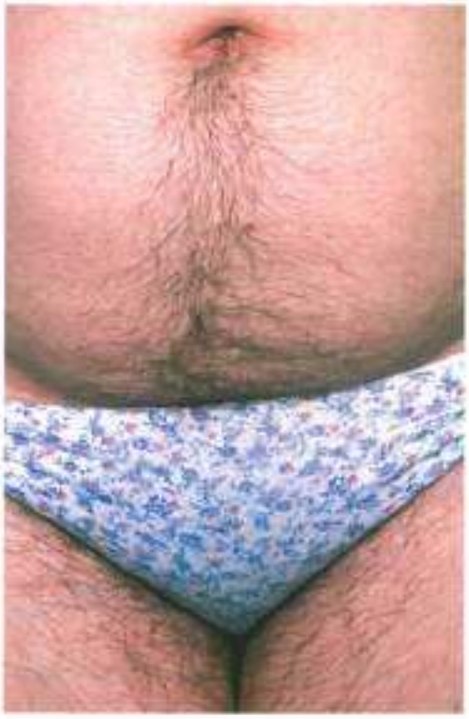


Fig. 26.8 Polycystic ovary syndrome. There is excess growth of terminal hairs in a male-like distribution, associated with irregular or absent periods, infertility, obesity and acne. These women often have insulin resistance, dyslipidaemia and hypertension (a 'metabolic syndrome'), with an increased risk of atherosclerosis.

Fig. 26.9 Pseudoacanthosis nigricans. There is a hyperpigmented velvety thickening of the skin of the flexures and neck, which is a cutaneous manifestation of insulin resistance.

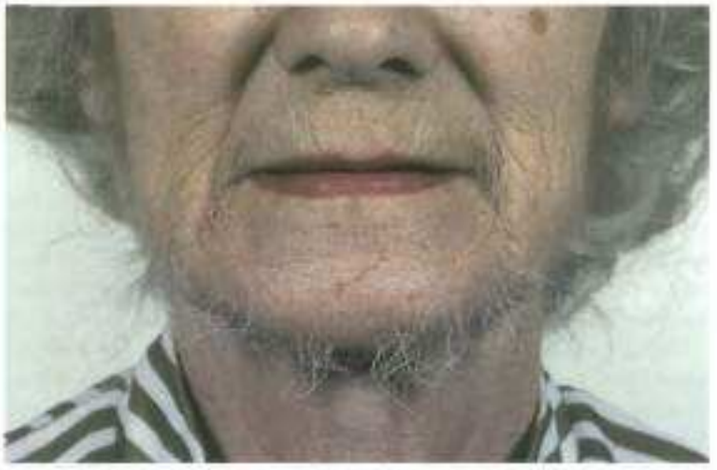


Fig. 26.10 Hirsutism. Excess growth of facial hair is common and physiological in females once oestrogen production diminishes after the menopause.

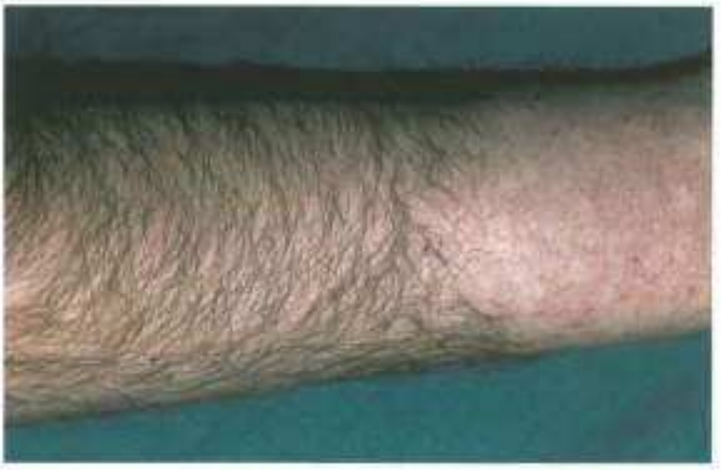


Fig. 26.11 Hirsutism treated by electrolysis. Electrolysis, although time-consuming, produces the most permanent results.

Once a cause has been excluded, the patient is labelled as having constitutional hirsutism. This is largely racial. It is rare in the Japanese and Chinese and common in Mediterranean, Middle Eastern, Indian and African races – although it is fair to say that most women develop some degree of hirsutism as they grow older, particularly after the menopause (Fig. 26.10) when the protective influence of oestrogens has been reduced. Racial hirsutism may be accepted as normal in the patient's own country but Western culture decrees that it is unnatural and the patient, therefore, regards it as unacceptable. Although males may be hirsute, and often bald as well, this is not considered a disease because it is socially acceptable.

The growth of the hair is thought to be caused by increased sensitivity of the hair follicle to dihydrotestosterone produced from testosterone by 5α-reductase (a similar mechanism to that of acne and male pattern alopecia). This may be the explanation of familial and racial hirsutism where the hormone tests are completely normal.

Clinical Features

Symptoms

Excess, unwanted dark hair.

Morphology

Overgrowth of terminal hairs.

Distribution

Upper lip (especially at the edges, producing a moustache), chin, sideburns, cheeks, around the areolae, sternum, limbs and lower abdomen (so producing a male escutcheon).

Management

The condition requires investigation, usually by an endocrinologist, if there is any clinical suspicion of virilism, which may lead to elucidation of the cause. The basic tests are full blood count, total and free testosterone, plasma cortisol at 9 a.m. and midnight, urinary 24-hour 17-hydroxy- and ketocorticosteroids, dehydroepiandrosterone sulphate, Δ-4-androstenedione, 3-α-androstanediol glucoronide, prolactin, SHBG (sex hormone-binding globulin) and luteinizing hormone/follicle-stimulating hormone levels (LH/FSH). Ovarian, adrenal and pituitary fossa scans may be necessary. The dermatologist is usually consulted regarding management of the unwanted hair. Treatment is not satisfactory, and this exacerbates the psychological distress to the patient. The traditional methods are:

- **Plucking** This is satisfactory for minimal involvement but is temporary.
- **Shaving** This is highly unsatisfactory and completely unacceptable to many patients, being final proof, to them, that they are not female.
- **Electrolysis** This is very satisfactory for limited disease (Fig. 26.11). A fine wire is passed down the hair follicle to cauterize and destroy the bulb. It must be performed skilfully, otherwise scarring occurs. It is time-consuming and expensive but in skilled hands is permanent.
- **Bleaching** Hydrogen peroxide, 10–20 vol. plus enough ammonia to turn litmus paper blue, is used to bleach melanin and also alter keratin. There are various proprietary preparations.
- **Depilatories** These consist of strontium or barium sulphide 20% in a suitable vehicle or thioglycollic acid. They are widely available commercially.
- **Waxing** This is very commonly used, especially for the legs.
- **X-rays** These have been used in the past and produce a permanent result, but there is a long-term risk of cutaneous and organ malignancy.
- **Lasers** Results at present are variable.
- **Systemic steroids** These are used to induce adrenal suppression.
- **Antiandrogens** These include:
  - Cyproterone acetate. It blocks the binding of dehydrotestosterone to the androgen receptor and due to its progesterone action inhibits the secretion of FSH and LH. It is available in the UK as a combination preparation containing 2 mg cyproterone acetate with 35 mcg ethinylestradiol (Dianette) and, therefore, has a contraceptive as well as a therapeutic effect. Usually larger doses are required and it is reasonable to prescribe 50–100 mg cyproterone acetate on days 5–15 of the cycle, in addition to the Dianette. The effect is not seen for 6–9 months, but there is some benefit in some patients.
  - Spironolactone is an antiandrogen that blocks the androgen receptor sites in the hair follicle as well as inhibiting androgen biosynthesis in steroid-producing cells. It has been shown to have an effect in the management of hirsutism, especially in the SAHA syndrome.
  - Drospirenone is a 17α spironolactone derivative with progestogenic, antiandrogenic and antialdosterone effects. It is used in combination with ethinyl estradiol.
  - Flutamide. This non-steroidal antiandrogen is used for benign prostatic hypertrophy. It may be helpful for adrenal SAHA and constitutional hirsutism.
  - Finasteride. This non-steroidal antiandrogen inhibits 5α reductase and may be of benefit in SAHA.

Telogen and anagen effluvium

Human hair grows in an asynchronous manner, unlike animal hair, which falls out synchronously as a moult. 'Moulting' only occurs in humans as part of a pathological state. There are three phases of growth during the human hair cycle. *Anagen* is the active and longest phase, lasting up to 4 or 5 years, which explains why hair will only grow to a certain length, usually to the waist or buttocks, but not down to the ground. The duration of anagen varies. It decreases with age on the scalp, is increased in the spring and diminished in the autumn. It is fastest on the chin and scalp and slowest in the axillae, on the thighs and in the eyebrows. The majority of the hair is in anagen at any one time. Following anagen, cell division ceases in the hair bulb and involution (*catagen*) occurs. The hair follicle regresses and the hair shaft becomes shortened and club-shaped. Catagen lasts a few weeks and is followed by *telogen*, during which hair is shed for about 3 months. The hair cell cycle is one of the most active in the body and is very susceptible to external influences. Telogen effluvium is described here.

Drugs used in cancer chemotherapy (Fig. 26.12) are now probably the most common causes of acute hair loss (*anagen effluvium*), which results from mitotic arrest of the cells of the hair bulb. The hair falls out within a few days but subsequently recovers.

The *loose anagen syndrome* affects girls (often less than 4 years old) with blonde hair. The hair is constantly shed, does not grow, is sparse, rarely if ever cut and easily pulled out. A trichogram reveals a misshapen bulb and ruffled cuticle. It is an autosomal condition of incomplete penetrance with a defect in keratin K6Hf, a type II cytokeratin found exclusively in the companion layer connected to the Henle layer via desmosomes.

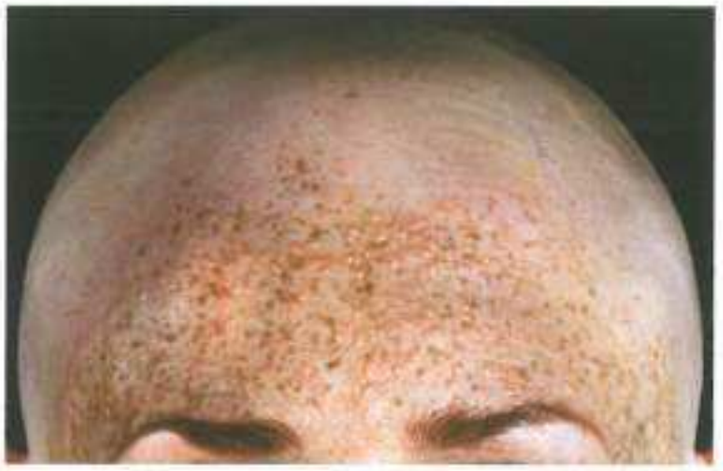


Figure 26.12 Anagen effluvium. This young lady shed all her scalp hair during conditioning for a bone marrow transplant for myelodysplastic syndrome. She presented with infections including viral warts (still evident on her forehead).

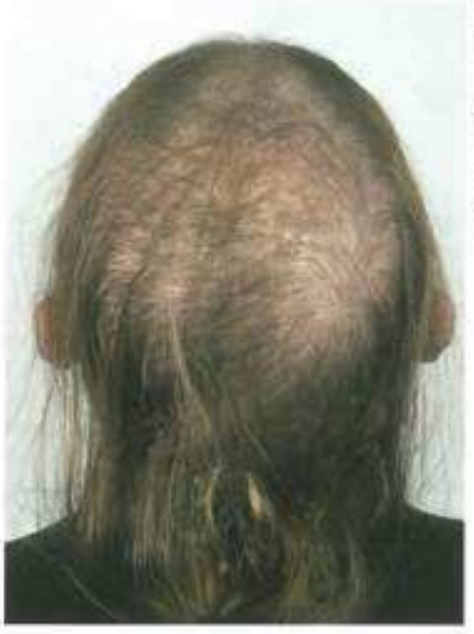


Fig. 26.13 Telogen effluvium. This woman developed a severe pustular exanthem secondary to amoxicillin therapy. Three months later, her hair fell out in an abrupt diffuse manner. She recovered completely within 12 weeks.

TELOGEN EFFLUVIUM

An acute, diffuse hair loss occurring 3–4 months after a medical event.

Aetiology

Surgical shock, haemorrhage (including occasionally blood donation), high fever, crash dieting and psychological illness are common causes. Women notice the complaint much more frequently than men. During the illness, anagen hairs are prematurely precipitated into catagen. Nothing untoward happens during this time, but as the hairs reach the telogen phase, new anagen hairs develop and displace the telogen hairs, causing them to fall abruptly and alarmingly.

A similar occurrence may occur after childbirth, particularly if complicated. The explanation in this case is slightly different. During pregnancy, hair grows luxuriantly because anagen hairs do not pass into the catagen phase but continue to grow until after parturition. Then all the hairs that should have gone into catagen during pregnancy do so and, 3 months later, fall out precipitously.

A number of drugs cause telogen effluvium, in particular thyroid antagonists (thioruracil or carbimazole), anticoagulants (heparin and coumarin), strontium ranelate and hypervitaminosis A. Thallium salts are tasteless and colourless and have been used as poisons by criminals and in the past by doctors for treatment of syphilis, tuberculosis and gonorrhoea. They produce a diffuse hair loss. Other side-effects are a crusted perioral dermatitis, a well-demarcated palmar plantar hyperkeratosis, Mee's lines (multiple parallel transverse white lines on the nails) and acute psychiatric and neurological and gastrointestinal symptoms. Thallium salts and X rays were also used specifically to produce loss of affected hairs in tinea capitis.

Clinical Features

Symptoms

The patient notices that hair comes out 'in handfuls', especially after being brushed or washed, and that the pillow case is covered in hairs in the morning, but does not associate it with any previous illness because of the time delay.

Morphology

The hairs are easily removed and the scalp is clearly visible (Fig. 26.13).

Distribution

The nails may also be affected and horizontal Beau's lines may be found.

Management

Explanation is all that is required, after taking a proper history, and reassurance that recovery will take place spontaneously within 3–4 months.

Diffuse hair loss

Congenital alopecia is rare but may be inherited as an autosomal dominant. Hypotrichosis may also be inherited in the same manner and may occur either at birth or at a later date during childhood. It may be associated with other ectodermal defects or hereditary syndromes, including the ectodermal dysplasias, progeria, Rothmund–Thomson syndrome and Netherton's syndrome. In addition, the hair may not only be sparse but also structurally abnormal (e.g. monilethrix and pili torti).

Fig. 26.14 Diffuse hair loss. This 46-year-old woman complained that her hair was falling out in handfuls. Her haemoglobin was 7 g/dl and she was iron deficient secondary to menorrhagia.

Diffuse acquired insidious loss of hair is a common complaint, particularly in females. The commonest cause is androgenetic alopecia. Occasionally the hair loss is caused by an associated illness (Fig. 26.14), particularly anaemia, endocrine disorders (myxoedema, hyperthyroidism, hypopituitarism or hypoparathyrodism), infections (including syphilis), immunological disorders (classically lupus erythematosus) and malnutrition (marasmus and kwashiorkor, malabsorption, iron deficiency, zinc deficiency or prolonged inadequate parenteral nutrition). Diffuse hair loss is a frequent complaint among young women (particularly from the Middle East) who usually have abundant long hair and where there is no objective evidence of hair loss. Blood investigations are normal and it may be a symptom of mild depression. The patient may be told that the hair is falling out but is being replaced at the same rate, so that all is in balance and no permanent alopecia will occur. Sometimes psychological assistance may be required.

MALE PATTERN ALOPECIA

A variable degree of loss of hair, with retention of parietal and occipital hair, which is inherited as an autosomal dominant.

Aetiology

The disorder is very common in males but also occurs in females, although to a lesser degree because of the protective influence of oestrogens. Similar abnormalities of androgen metabolism to those found in hirsutism occur. Males castrated prior to puberty never go bald, even in the presence of a strong family history.

Clinical Features

Pubertal male frontotemporal recession is normal, but this may be followed by frontal thinning (type I), some loss on the crown (type II) and various degrees of hair loss thereafter (Fig. 26.15), so leading to total baldness apart from the sides and back of the scalp. Eighty per cent of males will have developed at least type I baldness by the seventh decade. Some 15% eventually go completely bald and 1–2% are completely bald by the age of 30.

In females the picture is less obvious and less rapid in progress. The hair is fine and loss is diffuse across the vertex. Twenty-five per cent of women have type I loss by the age of 40, the condition being much more common than generally appreciated. Once the protective effect of oestrogens is lost after the menopause, hair loss may be marked (Fig. 26.16) but, paradoxically, hair may grow on the face.

Management

Most men know that there is no really good treatment for baldness, but this does not stop them from seeking it. Women tend to regard thinning of the hair as quite abnormal and do not appreciate the role of heredity. Treatment in women is unsatisfactory, but at least hormonal therapy with cyproterone acetate may be considered. Wigs are only popular with some patients as are hair transplants (Fig. 26.17), although the latter are commonplace in the USA. Plugs of hair taken from the occipital and parietal areas are used to replace the bald areas but the technique requires expertise and patience. The hairs fall out some weeks later but then regrow, although it may be 2–3 years before the hair begins to look 'normal'.

Topical minoxidil in a 2% or 5% solution is being used. The results are not dramatic but there certainly appears to be some increase in hair growth, particularly in patients who have only a limited loss and who have reported it early.

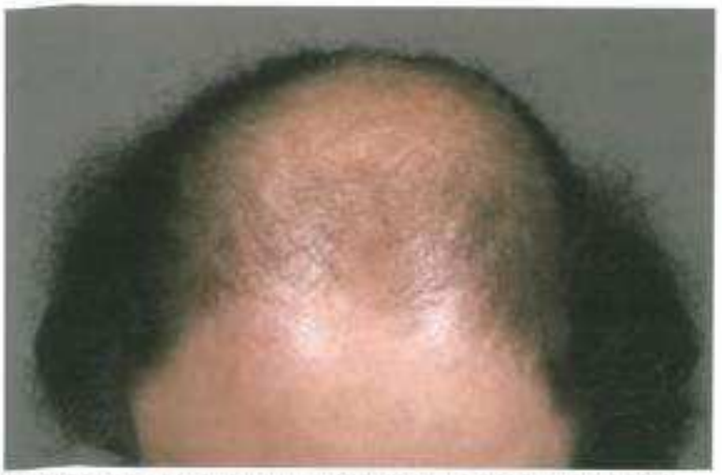


Fig. 26.15 Male pattern baldness. It is inherited as an autosomal dominant. Parietal and occipital hair remain despite total hair loss over the vertex.

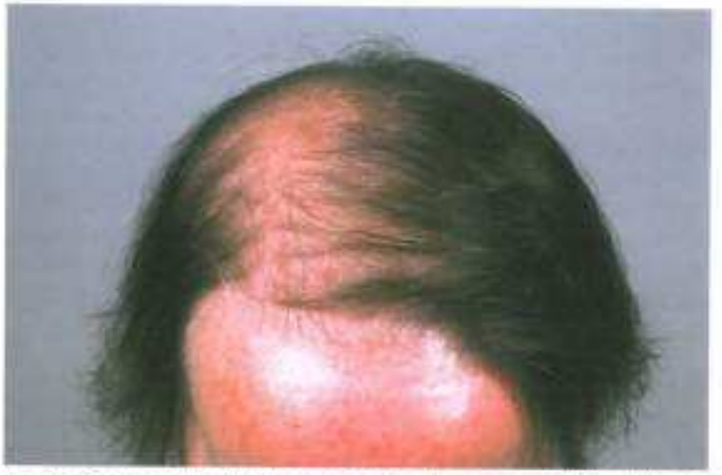


Fig. 26.16 Male pattern (androgenetic) alopecia in a female. This is inherited but does not usually become apparent until after the menopause.

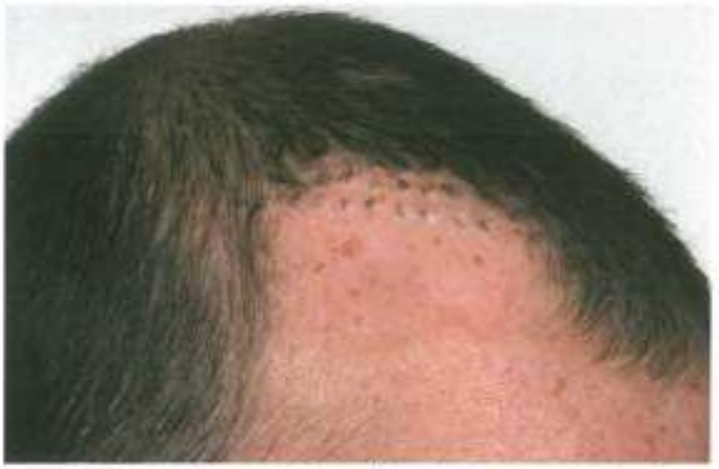


Fig. 26.17 Hair transplantation. Plugs of hair taken from the occipital and parietal areas are used to replace the bald areas.

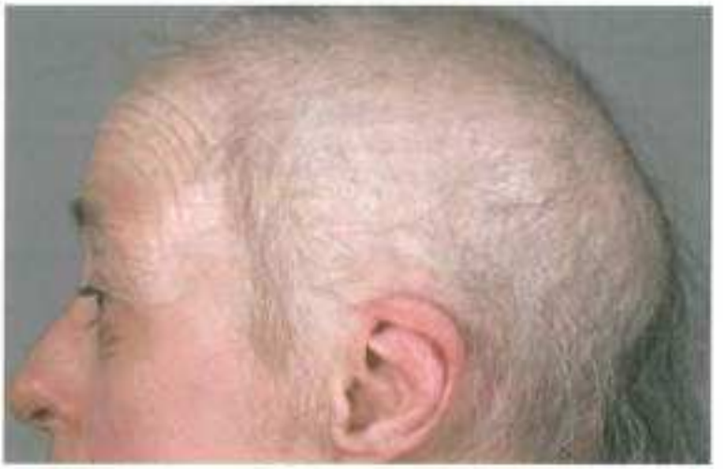


Fig. 26.18 Alopecia areata. This is more common in Down's syndrome and approximately half have alopecia universalis. Thyroid antibodies are regularly positive.

Men with decreased dihydrotestosterone levels owing to inherited 5α-reductase deficiency do not experience either the bitemporal recession that all males get or androgenic alopecia. Finasteride (Proscar) is a specific inhibitor of the type II 5α-reductase and reduces scalp and serum dihydrotestosterone levels in balding men at a daily dose of 1 mg. It is helpful in male pattern alopecia but it does need to be taken lifelong and there may be reduced libido and volume of the ejaculate.

Skin disorders affecting the hair and scalp

Tinea, psoriasis, dandruff, seborrhoeic eczema and pityriasis amiantacea have been dealt with in other chapters. Other disorders are described here.

ALOPECIA AREATA

A loss of hair with no appreciable abnormality of the underlying skin, ranging in severity from localized patches to universal involvement, caused by an organ-specific autoimmune T cell-mediated defect, which targets anagen stage hair follicles, leading to anagen arrest. Spontaneous recovery occurs in uncomplicated cases.

Aetiology

The disorder is common and affects both sexes equally. Anagen hair follicles express unique antigens; there are high levels of IgG antibodies to some of these antigens in most patients with alopecia areata. Similar antibodies have been demonstrated in mice with alopecia areata-like hair loss. Many patients have a personal family history of other autoimmune disorders, such as Hashimoto's thyroiditis and diabetes mellitus, as well as having organ-specific antibodies. Vitiligo is associated with 4% of cases and there is a positive family history of alopecia in 10% of cases of vitiligo. Histologically, there is a lymphocytic infiltrate around the hair follicles that comprises predominantly helper T-inducer cells (although suppressor/cytotoxic T cells have also been identified) and Langerhans' cells. This supports the autoimmune theory but, unlike other autoimmune disorders, there is no permanent destruction of the target organ and the hair may regrow. The condition is much more common in Down's syndrome (Fig. 26.18), where there is an incidence of 6% at any one time and a majority of these cases have alopecia universalis. It occurs in the autoimmune phase of the myelodysplastic syndrome and following reduced intensity conditioning (especially with campath) allogeneic bone marrow transplantation (Fig. 26.19).

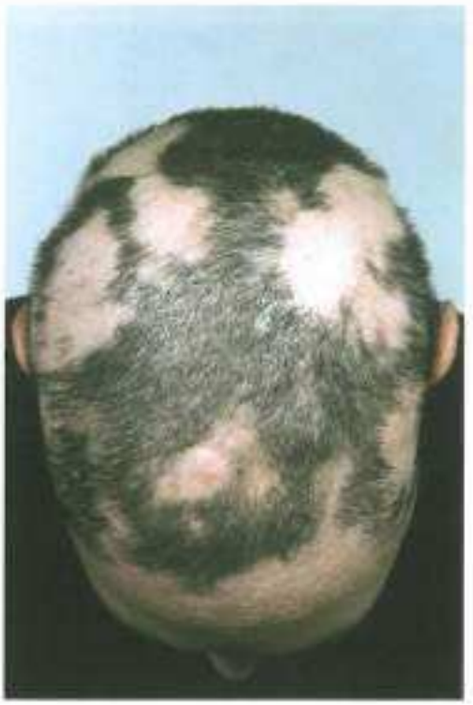


Fig. 26.19 Alopecia areata. This lady had refractory anaemia with excess blasts (RAEB), which was treated with a reduced intensity Campath conditioning allogeneic transplant. Autoimmune disorders commonly occur in association with myelodysplastic syndrome but Campath-associated autoantibody formation is well recognized.

Rare syndromes include:

- **IPEX** (immune dysregulation, polyendocrinopathy [diabetes mellitus, thyroiditis], enteropathy [antienterocyte antibodies], X-linked inheritance). It is due to a mutation of the FOX P3 gene which encodes a DNA-binding protein required for the regulation of T cells. The patients also have dermatitis and alopecia with nail involvement.
- **The 3H syndrome** Alopecia areata is associated with dysfunction of the hypothalamo-pituitary axis (isolated ACTH deficiency) and hippocampal-anterograde memory loss.

A number of patients have atopic eczema, and this is associated with a poor prognosis. Some report significant psychic trauma prior to the attack of alopecia. The condition is most common before the age of 40 but can occur at any time.

Clinical Features

Symptoms

Patches of hair loss (Fig. 26.20). Occasionally a patient complains of going 'white overnight'. This occurs in an adult who normally has a mixture of white and black hairs: the black hairs are preferentially shed and the white hairs remain, producing this startling effect (Figs 26.21 and 26.22).

Morphology

A single patch of hair loss is most usual but there may be several patches that are quite round with complete loss of hair and no visible change in the skin.

Distribution

Part of the scalp (Fig. 26.23), the whole scalp (totalis) or body (universalis) may be affected. The eyelashes (Fig. 26.24), eyebrows and beard area (Fig. 26.25) may be involved separately or in combination with the hair loss. Similarly, the secondary sexual hairs may be affected. The nails are involved in a minority of cases; pits occur, which are slightly larger than those in psoriasis. They are often found in longitudinal lines (Fig. 26.26).

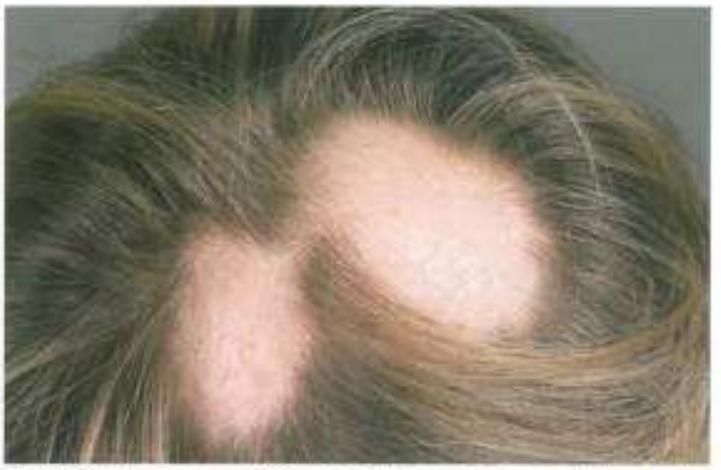
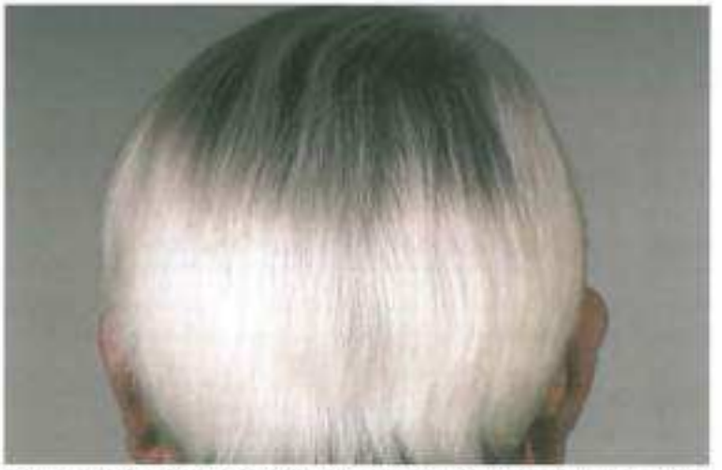


Fig. 26.20 Alopecia areata. The areas of hair loss are quite round with no scalp abnormality. The recovering hair is depigmented initially.



Figs 26.21 and 26.22 Alopecia areata. A patient may 'go white overnight'. This is caused by retention of the white hairs and preferential loss of pigmented hairs, which may be visible as the patient recovers (Fig. 26.22). This was said to happen to Queen Marie Antoinette, the night before she was guillotined (canities subita).

Management

The majority recover (Fig. 26.27) without any treatment within 9 months, especially those who have one or two patches and have never been afflicted before, but a number of other factors must be considered.

The onset of the disease in childhood causes the most concern. The patches may recover, but recurrent attacks and alopecia totalis or even universalis are a common outcome. Widespread involvement is also serious prognostically, with only a third or less of those with alopecia universalis recovering. The distribution is important: ophthiasis (occipital hair loss; Fig. 26.28) is always associated with a poor prognosis. Loss of eyebrows and eyelashes and associated atopic disease (especially eczema) augur poorly.

The features to be assessed in determining recovery are the presence or absence of exclamation mark hairs (Fig. 26.29) and the type of regrowth. Exclamation mark hairs are a few millimetres long. The stump appears normal but the proximal portion nearest the scalp is thin and depigmented. Exclamation mark hairs indicate continued activity of the disease and that the hair loss may deteriorate. As patients recover, fine white hairs appear and subsequently these become pigmented and return to their normal colour.

Fig. 26.23 Alopecia areata. The degree of hair loss varies. Occipital hair loss (ophthiasis) is associated with a poor prognosis.

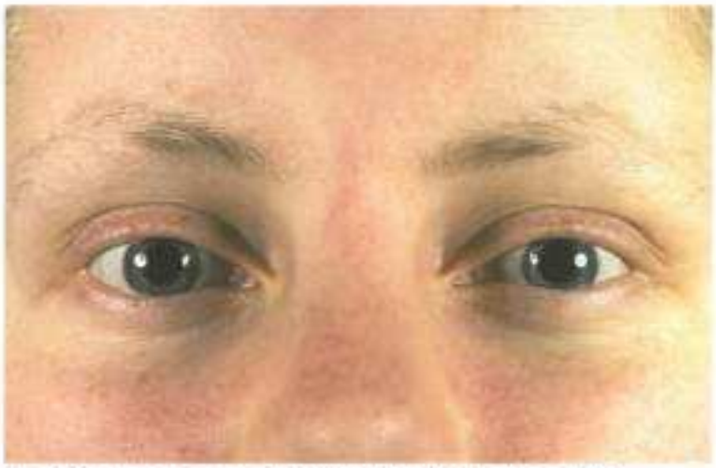


Fig. 26.24 Alopecia areata. Hair may be lost solely from the eyelashes.

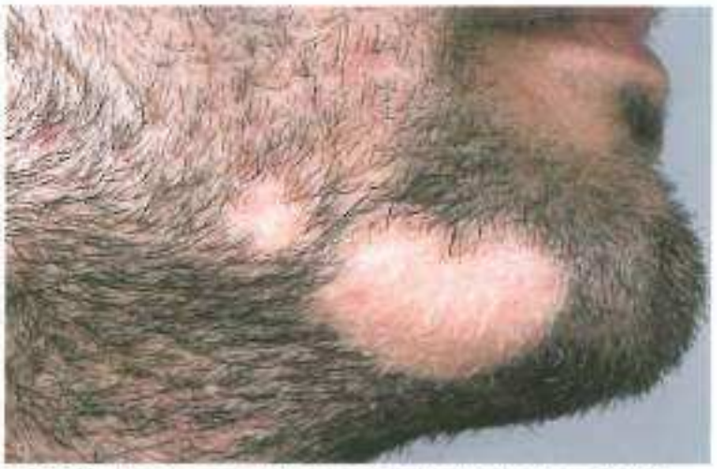


Fig. 26.25 Alopecia areata. Hairs may be lost from the beard area. The skin appears quite normal.

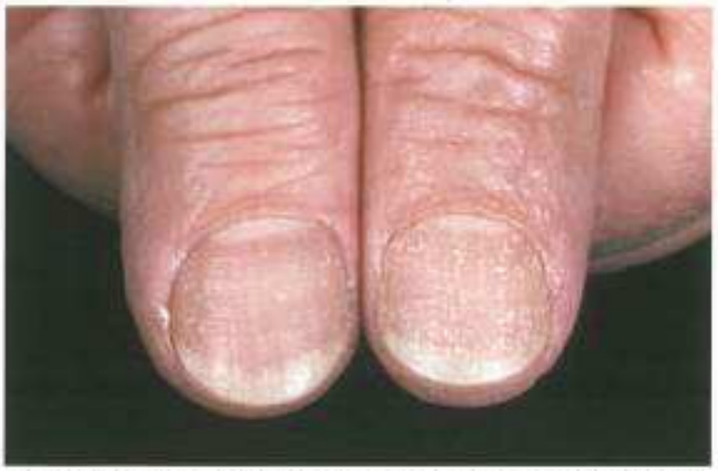


Fig. 26.26 Nail pitting in alopecia areata. In alopecia areata, the pitting occurs in a linear arrangement.

Fig. 26.27 Alopecia areata. Recovery usually occurs within a year, if there is a single patch of hair loss.

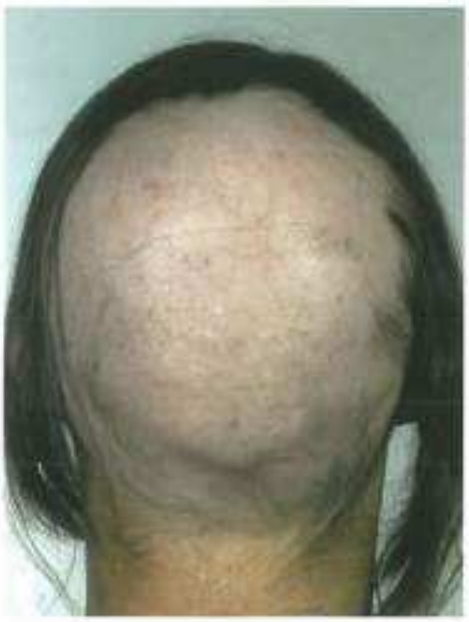


Fig. 26.28 Alopecia areata. Occipital loss of hair (ophiasis) is associated with a poor prognosis.

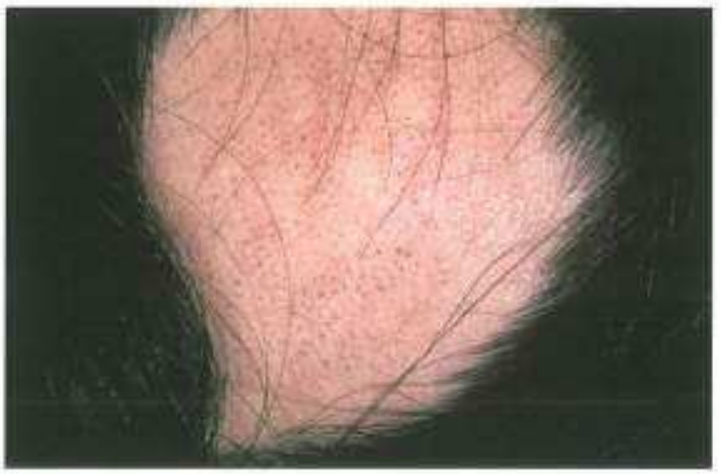


Fig. 26.29 Exclamation mark hairs. The stump appears normal but the proximal part near the scalp is thin and depigmented. These short ('exclamation mark') hairs indicate activity and that the hair loss will continue.

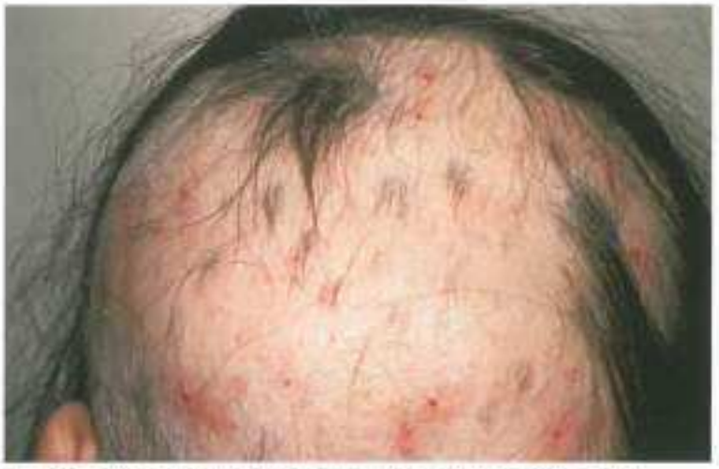


Fig. 26.30 Alopecia areata treated with intralesional steroids. Hair is regrowing at sites of previous injections. Fresh injection sites are also visible.

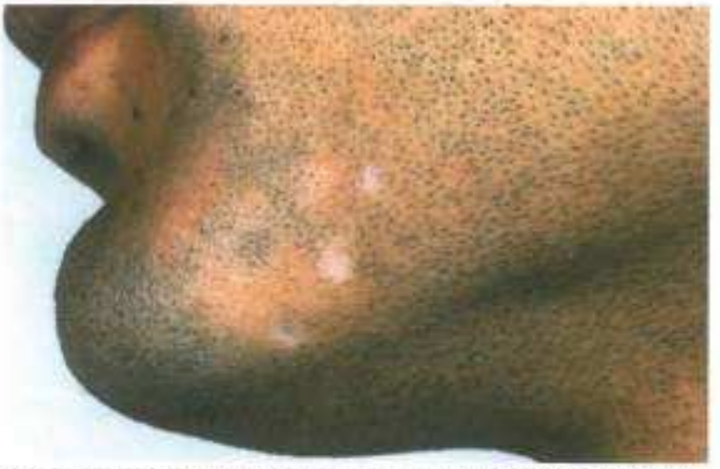


Fig. 26.31 Steroid atrophy and loss of pigmentation. These areas of dermal atrophy and loss of pigmentation have resulted from injections of triamcinolone.

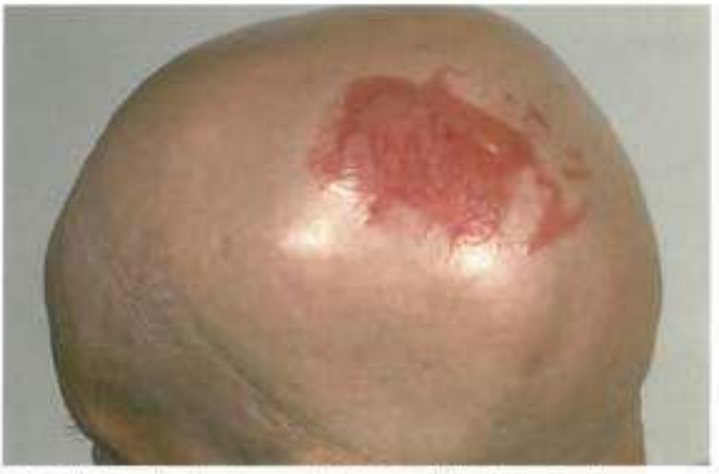


Fig. 26.32 Sensitization to a contact allergen. The skin is primed by application of a contact allergen (e.g. diphencyprone) on the arm and then applied to the scalp to induce a dermatitis.

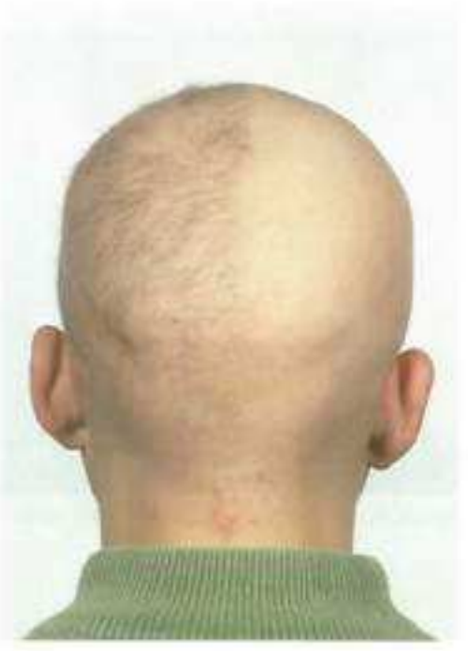


Fig. 26.33 Immunotherapy for alopecia universalis. The left side of the scalp was treated with diphencyprone, using the right as a control. Similar results are sometimes achieved with superpotent topical steroids.

The results of specific treatment are always difficult to assess since the majority of cases resolve spontaneously, but therapies include:

- **Steroids** The standard treatment is topical steroids or intralesional triamcinolone. Systemic steroids are effective and have been used for alopecia universalis, but the hair usually falls out at the cessation of treatment and the risks involved in therapy are unacceptable. Intralesional steroids produce a convincing picture of hair growth in the site of the injections (Fig. 26.30), but subcutaneous atrophy is a potential side-effect (Fig. 26.31), particularly in the beard area where they should be avoided. Topical potent glucocorticosteroids applied each night for 3 months are probably the treatment of choice if any treatment is indicated.
- **Irritants and sensitizers** Dithranol (Anthralin), a classical treatment for psoriasis, is a potent irritant of the skin, and some success has been claimed for applications of this drug to areas of alopecia. Dinitrochlorobenzene (DNCB) is a potent contact allergen, producing a contact dermatitis after the patient has been primed (Fig. 26.32). The dermatitis is unpleasant, as it is acute and weeping, often with regional lymphadenopathy. However, it can be successful (Figs 26.33–26.35). Diphencyprone has replaced DNCB since it is considered to be a potential carcinogen to the skin. Primin (which is the sensitizer in *Primula obconica*) and poison ivy, which is the common cause of plant dermatitis in North America, have been tried. All these remedies are unpleasant and should probably only be used by a dermatologist. The results vary.
- **Ultraviolet light** Irradiation with ultraviolet B in order to cause erythema is a time-honoured treatment. In recent times, psoralens and ultraviolet A (PUVA) have been used with variable results.
- **Minoxidil** About a third of patients with extensive alopecia areata will respond to topical minoxidil.
- **Ciclosporin** A small proportion of patients with extensive alopecia areata have been treated successfully.
- **Tacrolimus** Topically results have been very variable.

The diagnosis is straightforward because the skin itself is completely normal. However, in the differential diagnosis should be considered:

- Tinea capitis (Fig. 26.36).
- Lupus erythematosus
- Congenital absence of the skin (Fig. 26.37).

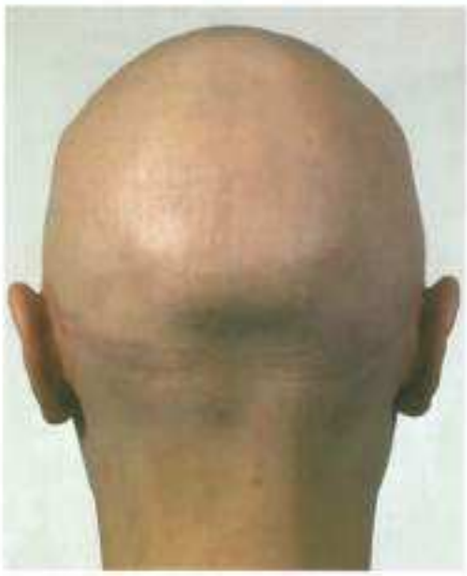


Fig. 26.34 Alopecia universalis.
The prognosis for recovery of universal alopecia is poor.

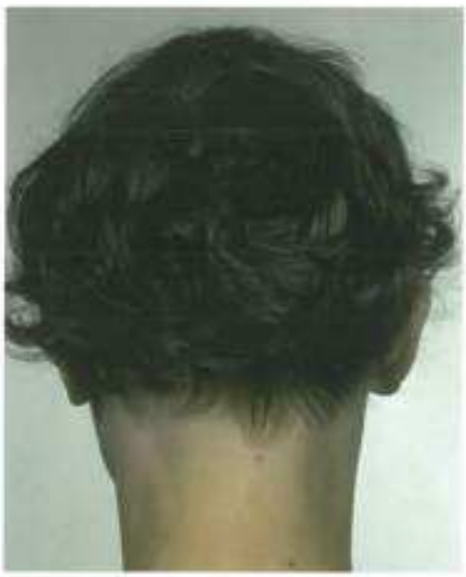


Fig. 26.35 Alopecia universalis.
This woman's universal alopecia (Fig. 26.34) recovered completely with dinitrochlorobenzene. This is exceptional. The hair began to fall out in patches 4 years later.

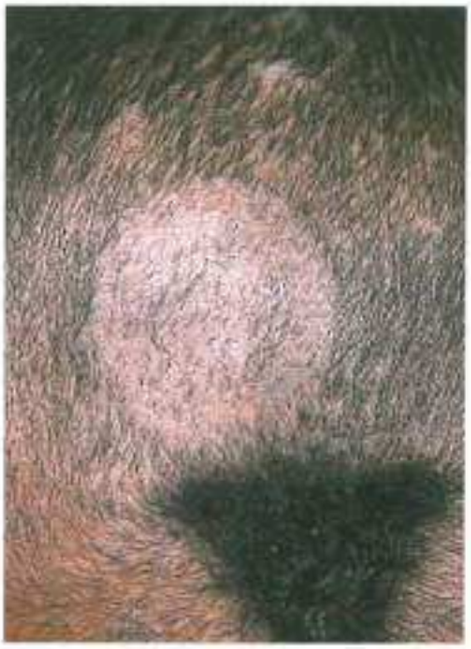


Fig. 26.36 Tinea capitis.
Children with patches of alopecia may have ringworm. It is currently occurring in epidemic proportions, particularly from contaminated barber's equipment. There is minimal inflammation, but the hairs are broken off at different lengths.

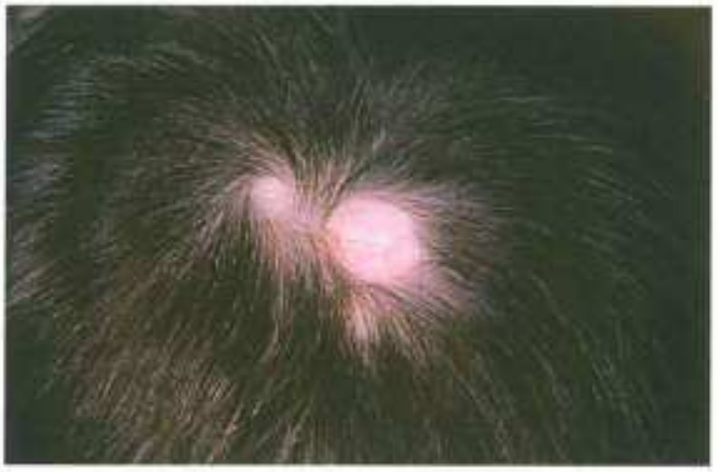


Fig. 26.37 Congenital absence of the skin. This was present from birth (most unlikely in alopecia areata) and the skin has healed with scarring. It is most common on the scalp and may be associated with neurological and other developmental anomalies.

PITYRIASIS AMIANTACEA

A distinctive morphological entity of thick scales attached to the hair shaft, sometimes secondary to seborrhoeic dermatitis or psoriasis.

Aetiology

It is common in children and young adults; the cause is unknown but in some cases is a manifestation of psoriasis or seborrhoeic eczema.

Clinical Features

Symptoms

A severe rash on the scalp.

Morphology

There is a considerable build-up of scales, which appear to be attached to the lower part of the hair shaft, rather like tiles overlapping on a roof (Fig. 26.38).

Distribution

Scalp.

Fig. 26.38 Pityriasis amiantacea. Thick scales are attached to the hair shaft. The condition does not respond to topical steroids but it does to tar-containing medicaments. Temporary hair loss usually follows.

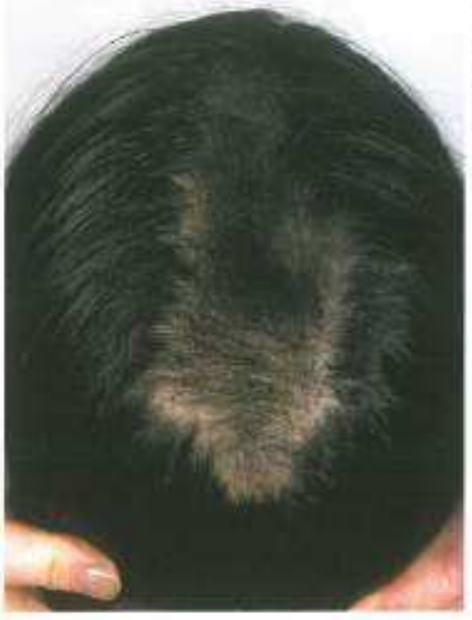


Fig. 26.39 Trichotillomania. Asymmetrical loss of hair secondary to pulling and twisting is a common temporary habit in children. The broken hairs are of uneven lengths.

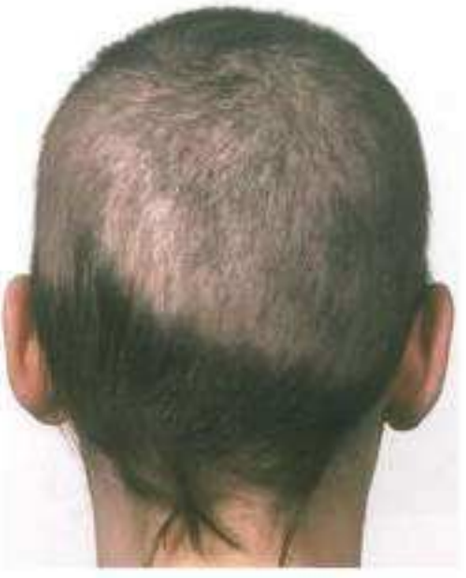


Fig. 26.40 Trichotillomania. The hair loss may be extensive. Tactful questioning of the child and parents may elucidate the cause of the underlying emotional disturbance.

Management

The condition does not respond to topical steroids. Tar-containing ointments such as ung. cocois co. (cocois) are effective. Although many of the affected hairs fall out, this is temporary and replacement occurs. For many it is a single episode, but if it does recur, an underlying psoriasis or seborrhoeic dermatitis should be suspected.

TRICHOTILLOMANIA

A fanciful name to describe a condition of self-induced hair loss.

Aetiology

This is a disorder primarily of children. It does not usually represent any deep emotional trauma but is a temporary habit tic, rather like nail-biting. It results from the child fiddling, twisting and pulling at the hairs, causing them to fall out or break off. It does occur, though less commonly, in adults when depression, unhappiness or psychosis is usually present. The prognosis is poor in the latter.

Clinical Features

Symptoms

Hair loss.

Morphology

There are one or more asymmetrical patches of hair loss (Fig. 26.39). The hairs are broken off at various lengths above the surface, without any inflammatory changes in the scalp.

Distribution

The side of scalp affected usually corresponds to the dominant hand of the patient. In severe cases and in adults the pattern is that of a tonsure with retention of the frontal hair (Fig. 26.40).

Management

The histopathology is characteristic and distinguishes it from alopecia areata. There are pigmented casts in the superficial segment of the hair follicle. They are displaced pigment cells from the hair matrix secondary to the traction. Once it is recognized that the condition is self-induced, it is necessary to assess the degree of emotional disturbance and treat accordingly.

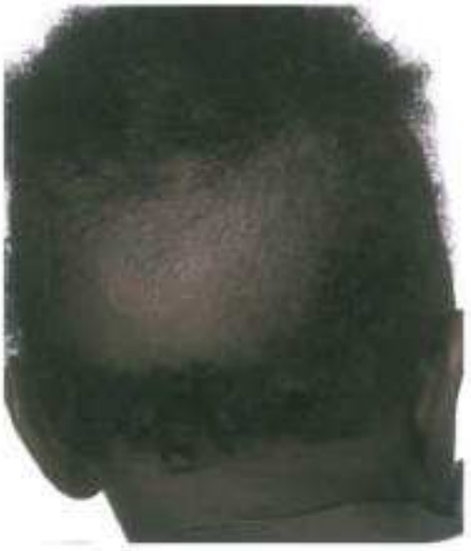


Fig. 26.41 Traumatic alopecia. This is common in infancy over the occiput, probably from friction. It recovers.

TRACTION ALOPECIA

A localized hair loss usually secondary to an unsuitable method of hair styling.

Aetiology

Any manner of trauma may damage the hair including overzealous massage of the scalp, permanent waves or straightening hair with hot combs. A malfunctioning hair dryer may cause uneven hair fractures secondary to burns. Infants temporarily lose the hair over the occiput from rubbing it whilst lying on their backs in their cot (Fig. 26.41). Frontal marginal alopecia caused by the hair being pulled back too tightly in a ponytail over a long period of time is fairly obvious. Blacks frequently plait their hair; if this is done incorrectly and too much traction is exerted on the hair and its follicle, the hair becomes thin, barely attached and eventually breaks away.

Clinical Features

Symptoms

The patient, usually female, complains of hair loss.

Fig. 26.42 Traction alopecia. There are scattered patches of alopecia. The remaining hairs can be seen to be gathered up into tight collections where they are under considerable tension.

Fig. 26.43 Traction alopecia. The hair styling has involved plaiting the hair and the hair at the sides of the bands are thinned and weakened by the undue traction on the hair root.

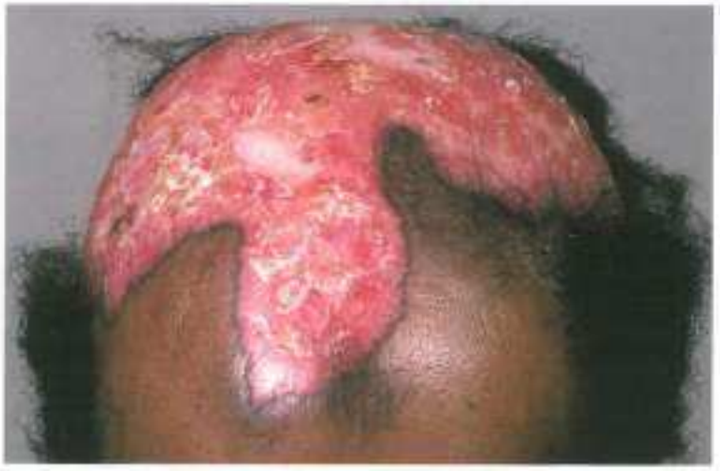


Fig. 26.44 Scarring alopecia. Discoid lupus erythematosus may result in well-defined, red patches with tenacious scales, scarring and hair loss.

Fig. 26.45 Follicular lichen planus. There is erythema and hyperkeratosis at the edge of the alopecia. Biopsy shows the specific lymphocytic histology of lichen planus, which is responsive to immunosuppressive drugs.

Morphology

There is hair loss surrounding islands of fractured hairs (Fig. 26.42) without scalp abnormality. The traction on the hair may be obvious (Fig. 26.43).

Distribution

The scalp.

Management

The hairstyle that was the cause may have been abandoned because the nature of the problem was suspected, but surprisingly it may not be accepted as the correct diagnosis by the patient. It needs careful explanation, but frequently it is recognized too late or the patient may be unwilling to abandon this traditional hairstyle. Regrettably the hair loss is often permanent.

SCARRING ALOPECIA

This is the end stage of any inflammatory process which destroys the hair follicle causing scarring and permanent hair loss. Pseudopelade and tufted folliculitis are alternative names sometimes used interchangeably for this. It is classified into three groups, based on the pathology of the inflammatory infiltrate.

Lymphocytic group

- **Chronic discoid cutaneous lupus erythematosus** (Fig. 26.44), characterized by follicular plugging and central inflammation with an adherent scale.
- **Lichen planopilaris**. There are three putative clinical types:
  a) *Follicular*. This is characterized by erythema and hyperkeratosis at the edge of the alopecia (Fig. 26.45).
  b) *Frontal fibrosing alopecia of Kossard*. An early postmenopausal alopecia of the frontal and temporal hair line with a pale band of skin lacking follicular ostia but manifesting scarring. There is perifollicular erythema and loss of eyebrows. There is a lymphocytic infiltrate around the isthmus and infundibular regions. It may be a variant of lichen planus, because it is occasionally associated with it. It may or may not progress and it is not clear whether treatment with systemic steroids alters the cause of the disorder.

Fig. 26.46 Pseudopelade. The cause of this scarring alopecia is unknown. The scalp is punctuated by islands of tufts of hairs growing out of the scarred areas. (Courtesy of the Institute of Dermatology.)

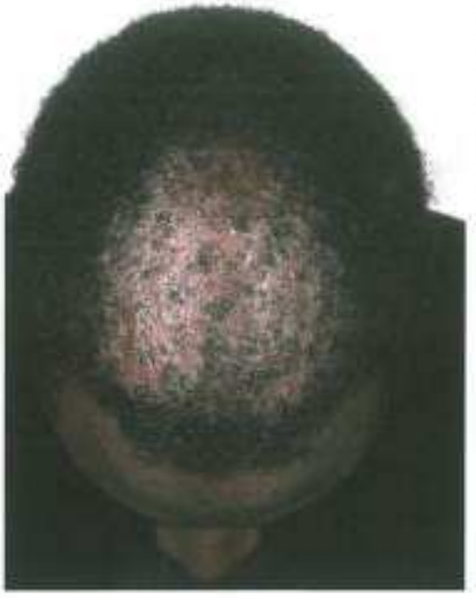


Fig. 26.47 Central centrifugal cicatricial alopecia. Sometimes known as 'hot comb alopecia', it affects the vertex and crown of the scalp of Afro-Caribbeans and African-Americans who use chemical hair relaxants and hot combs. It is usually associated with *S. aureus*.

c) *Graham–Little disease* (Ch. 7). A rare triad of progressive scarring of the scalp, but non-scarring loss of pubic and axillary hair with widespread keratosis pilaris and skin-coloured follicular papules over the forehead and scalp.

- **Pseudopelade of Brocq** There are multifocal asymptomatic flesh-coloured patches of cicatricial alopecia, often described as 'footprints in the snow' (Fig. 26.46). The cause is unknown.
- **Central centrifugal cicatricial alopecia** This is quite common in Afro-Caribbeans and African-Americans. They have usually used chemical hair relaxants and hot combs (also known therefore as *hot comb alopecia*). It affects the crown and vertex (Fig. 26.47) and may be associated with *S. aureus*-positive pustules (and labelled folliculitis decalvans). Others are less inflammatory and more indolent and labelled pseudopelade. It is chronic and progressive, although it ultimately remits.
- **Alopecia mucinosa** (Ch. 12).
- **Keratosis follicularis spinulosa decalvans** This starts in infancy, progressing to scarring in childhood and adolescence. It is accompanied by widespread keratosis pilaris, especially on the face.

Neutrophilic group

- **Folliculitis decalvans** (see below).
- **Dissecting folliculitis of the scalp** (see below).

Mixed inflammatory group

- **Acne keloidalis nuchae** (see below).
- **Acne necrotica varioliformis** This is a chronic condition, which occurs from the third decade onwards. There are recurrent crops of erythematous papulopustules which undergo central necrosis and form scars of oedematous, umbilicated lesions which become crusted and leave a varioliform scar. They occur on the anterior scalp, eyebrows, nose, neck and chest. The differential diagnosis is acne necrotica miliaris (although probably a variant), which occur as intensely itchy follicular vesiculopustules which do not scar.
- **Erosive pustular dermatosis** (see below).

There are also causes of scarring alopecia, which do not fit the above classification, but fortunately their cause is well understood. These include:

- **Pemphigus** (Fig. 19.36)
- **Mucous membrane pemphigoid** (Fig. 26.48)
- **Favus** (Ch. 15)
- **X-irradiation of the scalp** previously employed to treat ringworm (Fig. 26.49).

DISSECTING CELLULITIS OF THE SCALP

A rare chronic suppurative disorder of the scalp that occurs particularly in young males of African descent.

Aetiology

This unusual condition, also known as *perifolliculitis capitis abscedens et suffodiens*, may occur alone or in association with acne conglobata and suppurative hidradenitis. There is a defect in follicular keratinization leading to portal obstruction and accumulation of sebaceous and keratinous material within the dilated pilosebaceous units, which rupture and evoke an intense neutrophilic inflammatory reaction with abscess and sinus tract formation. There may be secondary bacterial infection with opportunistic strains (*P. acnes* and coagulase-negative staphylococci) and occasionally pathogenic strains of *S. aureus*.

Clinical Features

Symptoms

A painful condition of the scalp, which discharges purulent material.

Morphology

There are firm, tender, fluctuant, grouped nodules (Fig. 26.50) that intercommunicate and form undermining draining sinuses and abscesses (Fig. 26.51) and ultimately cerebriform ridges (Fig. 26.52). Hair is absent on top of the nodules following the discharge of pus from the follicles but is present in the clefts in between. Scarring and keloid formation may result.

Distribution

The vertex and occiput are especially affected.

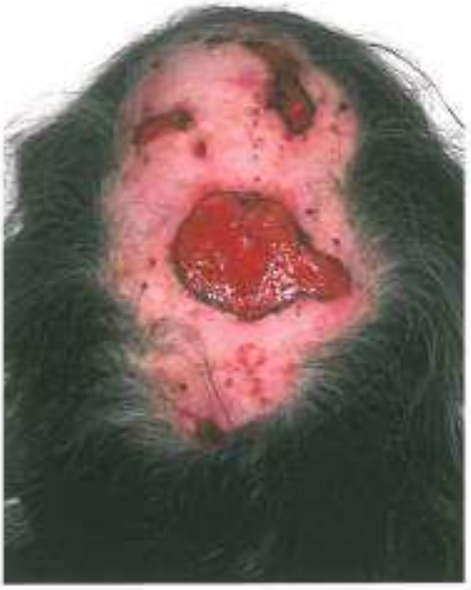


Fig. 26.48 Mucous membrane pemphigoid. Blisters and ulceration lead to scarring alopecia in mucous membrane pemphigoid.

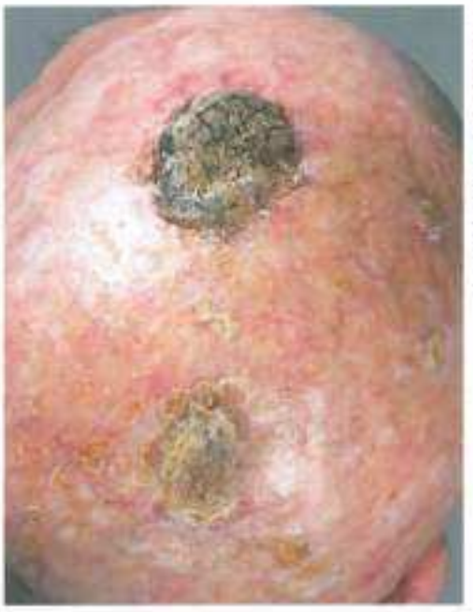


Fig. 26.49 Scarring alopecia. Ringworm of the scalp used to be treated with radiotherapy to induce epilation of the affected hairs. This invariably resulted in a scarring alopecia. Sometimes radionecrosis and malignant neoplasms develop many decades later, as here.

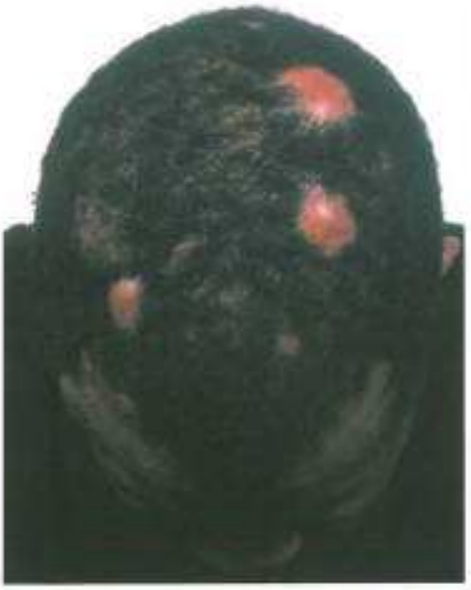


Fig. 26.50 Dissecting cellulitis of the scalp. There are firm tender fluctuant hairless nodules which intercommunicate and form sinuses and abscesses and cerebriform ridges.

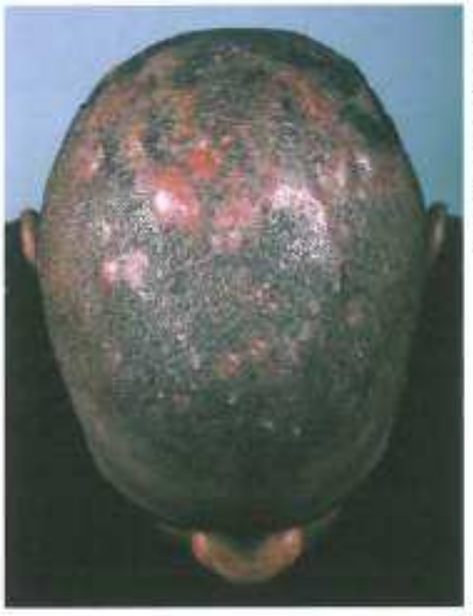


Fig. 26.51 Dissecting cellulitis of the scalp. This is a rare chronic suppurative disorder of the scalp, which occurs primarily in males of African descent sometimes in association with acne conglobata and hidradenitis.

Management

A biopsy may be helpful and tinea should be excluded. It should be distinguished from *lipedematous scalp* where the scalp feels boggy but there are no abscesses. It occurs in black females. The scalp is twice its normal thickness secondary to oedema and expansion of the subcutaneous fat. It may lead to alopecia.

13-*cis*-Retinoic acid has made a substantial contribution to the treatment of the condition. Adalimumab is also effective, but the condition may relapse afterwards. Occasionally in chronic cases, squamous cell carcinoma may eventuate.

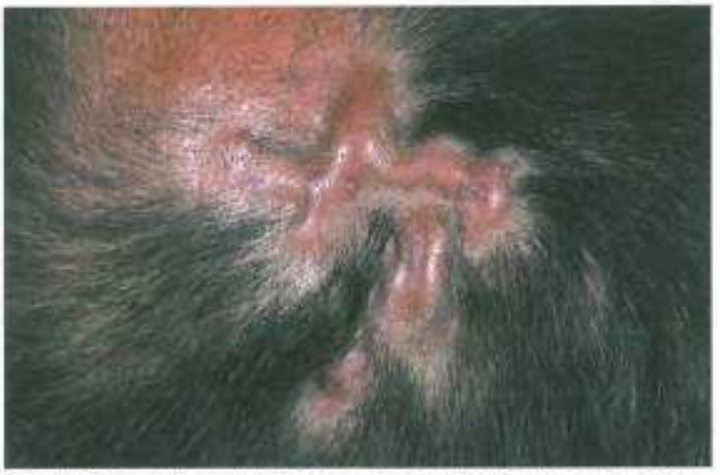


Fig. 26.52 Dissecting cellulitis of the scalp. Firm, tender, grouped nodules coalesce to form hairless ridges with hair growing in the clefts between. It does respond to 13-*cis*-retinoic acid.

FOLLICULITIS DECALVANS

A chronic folliculitis that eventuates in progressive scarring of the scalp.

Aetiology

Although hot comb alopecia may result in a similar state, some reserve this term for an uncommon progressive purulent (*S. aureus*) condition (Fig. 26.53) of any hair-bearing sites. The cause is not certain. It may be a form of seborrhoeic eczema or a local immunological failure. Histology shows follicular abscesses with polymorphonuclear infiltrate, followed ultimately by scarring. It is common in Africans and Afro-Caribbeans.

Clinical Features

Symptoms

A painful discharging eruption usually of the scalp but of any hair-bearing area.

Morphology

There are painful follicular pustules which crust and result in a patchy alopecia expanding outwards from the area of folliculitis. The scalp becomes boggy and indurated. The end result is of multiple tufts of hair coming out of a common dilated follicular opening rather like 'doll's hair'.

Distribution

The scalp (particularly vertex), but any hair-bearing area may be involved.

Management

A swab should be taken from the pustules and from carrier sites for culture and sensitivities. The condition does respond to antibiotic therapy but tends to occur on stopping treatment. Rifampicin (very lipid soluble and, therefore, well absorbed into the skin) is effective, particularly in combination with clindamycin for 10 weeks.

EROSIVE PUSTULAR DERMATOSIS OF THE SCALP

A chronic disorder of the scalp that occurs in the elderly.

Aetiology

The cause is not known but it may represent the end-result of chronic trauma and, in particular, from ultraviolet irradiation. It is most common in elderly females. The histology shows chronic inflammation in the dermis and areas of epidermal erosion.

Clinical Features

Symptoms

Sores on the scalp.

Morphology

Erosions of the skin and crusts result from superficial pustules (Fig. 26.54). Scarring may result and squamous cell carcinoma may develop in the scars.

Distribution

There is usually male pattern thinning of the hair of the scalp and the changes occur within this area.

Management

The condition requires historical differentiation from radiodermatitis arising from previous treatment of scalp ringworm. The condition tends to be recurrent and chronic but does respond to superpotent steroids combined with antibiotics. Zinc sulphate 200 mg twice daily is worth trying.

Fig. 26.53 Folliculitis decalvans. This is a staphylococcal folliculitis with oozing yellow pustules which ultimately result in a scarring (including keloids) alopecia. It is often seen in Africans, Afro-Americans and Afro-Caribbeans.

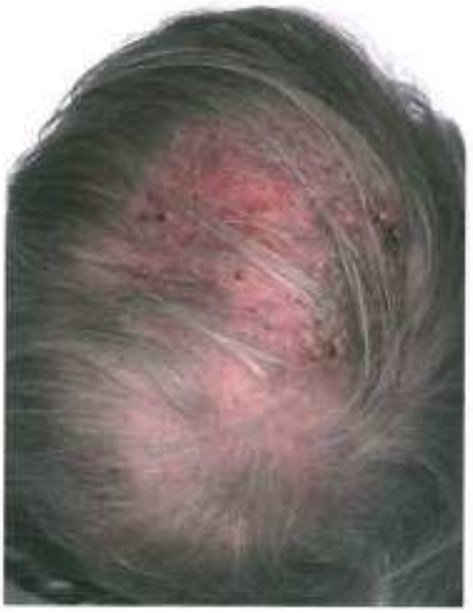


Fig. 26.54 Chronic erosive pustulosis of the scalp. Pustules and crusting occur on the scalp. There is male-pattern thinning, as in this elderly woman, and the condition is thought to be secondary to solar damage and trauma.

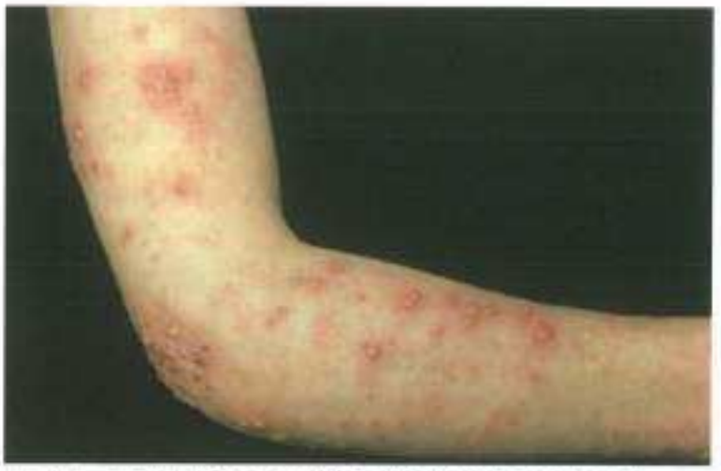


Fig. 26.55 Folliculitis. This is a septic folliculitis caused by potent topical glucocorticosteroids used to treat a patient with infected eczema.

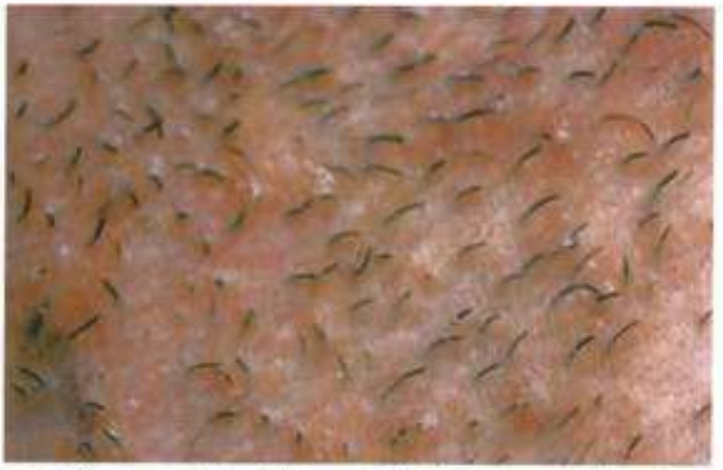


Fig. 26.56 Ingrowing hairs (pili incurvati). This is a common condition and gives rise to a sterile folliculitis.

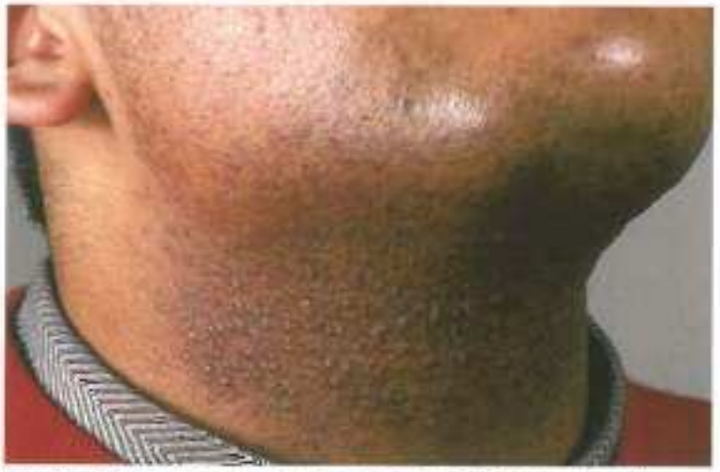


Fig. 26.57 Folliculitis caused by ingrowing hairs. This is common on the neck, particularly in those with strong beard growth.

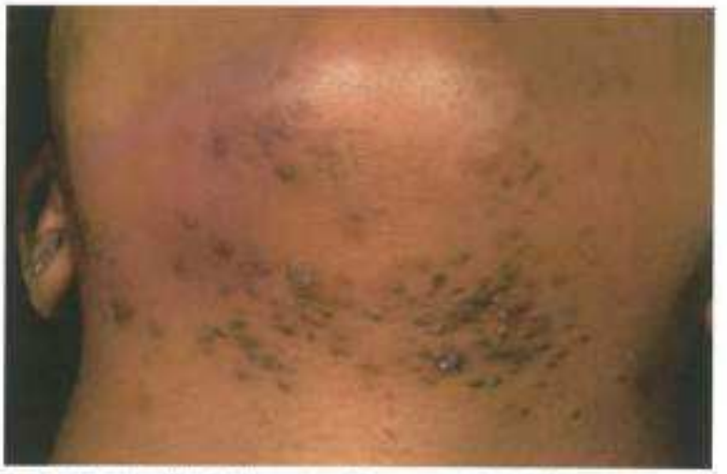


Fig. 26.58 Folliculitis. The ingrowing hairs may result in keloid formation as in this hirsute Afro-Caribbean lady.

FOLLICULITIS

Folliculitis is an inflammatory disorder of the hair follicle.

Aetiology

Folliculitis may be septic or sterile. Septic folliculitis of the beard area is known as *sycosis barbae* (Ch. 13). The hair-bearing skin on the limbs or torso may be affected, particularly in association with the use of topical glucocorticosteroids (Fig. 26.55). A swab will establish the diagnosis in these cases and they are dealt with elsewhere.

There are a number of disorders associated with a sterile folliculitis. The most common is probably caused by ingrowing hairs (Fig. 26.56) and is seen in those with strong beard growth, particularly under the neck (Fig. 26.57). This pseudofolliculitis is frequently associated with sterile follicular pustules on the limbs, particularly the thighs. These individuals are usually hirsute and the condition may be precipitated by occlusion of any sort, but particularly tight-fitting jeans. It may be exacerbated by an occupation in which the clothing becomes contaminated with oil. Many of these patients also have a tendency to acne. In black patients, keloid formation frequently follows the inflammation secondary to ingrowing hairs (Fig. 26.58). This is seen at the back of the neck and is known as *acne keloidalis* (Fig. 26.59), but it may occur throughout the scalp if the head

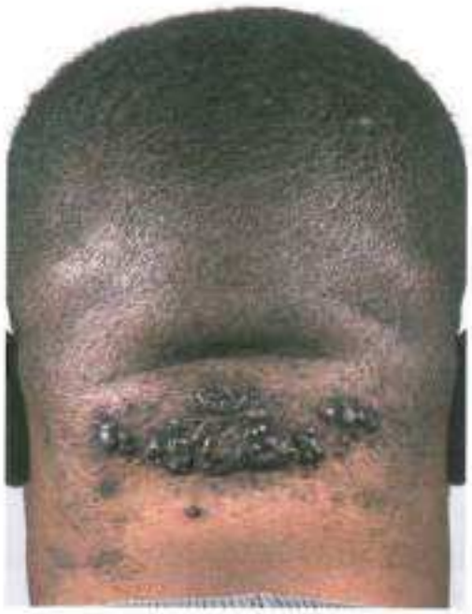


Fig. 26.59 Acne keloidalis nuchae. The classical site for keloids secondary to folliculitis from ingrowing hairs is the back of the neck. Treatment is very unsatisfactory.

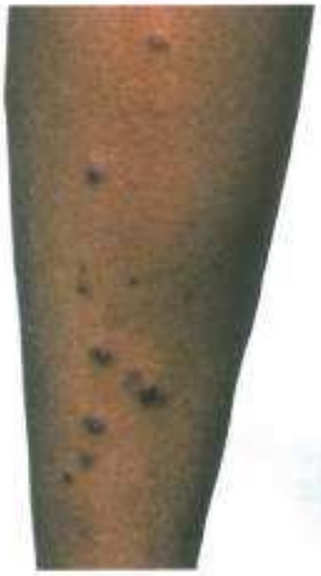


Fig. 26.60 Acquired perforating folliculitis. This occurs in association with end-stage renal failure and diabetes and the histopathology shows extrusion of connective tissue through the epidermis.

has been shaved at any stage. In this situation, the folliculitis is not only caused by the ingrowing hairs but may also be a consequence of sepsis introduced by the barber's razor.

Acquired perforating folliculitis of the limbs with chronic renal disease and diabetes mellitus (Fig. 26.60) and *eosinophilic folliculitis* associated with the acquired immunodeficiency syndrome (AIDS) are described in Chapters 20 and 14 respectively.

Clinical Features

Symptoms

Unsightly painful inflamed spots around the hairs.

Morphology

White or yellow pustules with a central hair and surrounding inflammation.

Management

Swabs should be taken, to exclude a septic folliculitis, from the pustules and also from the staphylococcal carrier sites in the nose, axillae, groin and perineum. There is no really successful treatment for ingrowing hairs other than to grow a beard, which is not always acceptable to the patient. Low-dose antibiotics given in a similar manner as for the treatment of acne may be helpful for some and topical antibiotics are also employed.

Structural defects of hair

Structural defects are important because they are often hereditary and may indicate an acquired metabolic disorder, for example trichorrhexis nodosa (arginosuccinicaciduria, citrullinemia and others), trichoschisis (trichothiodystrophy), trichorrhexis invaginata (Netherton's syndrome), monilethrix and pili torti (various). The hair is usually fragile and varying degrees of alopecia result. Structural defects may occur without increased fragility, for example:

- **Pili annulati** The hair is characterized by a striking ringed appearance resulting from alternating light and dark bands (Fig. 26.61); the abnormal dark regions are caused by multiple cortical air spaces, which can be seen under polarized light (Fig. 26.62). It may occur sporadically or as an autosomal dominant. It presents in infancy. There are no systemic associations and no hair fragility. It is only clinically detectable in fair or blonde hair.
- **Woolly hair syndromes** of coiled or wavy hair in a localized or universalis distribution in a Caucasian. The average curl diameter is 0.5 cm. It may be associated with cardiac abnormalities (Naxos disease), skin fragility and keratoderma.
- **Uncombable hair syndrome** In the latter, electron microscopy of the hair shows it to be triangular in cross-section with a groove along one side. The hair is unmanageable and often a distinctive silvery blonde colour (Fig. 26.63).
- **Curly hair** These are large, loose spiral locks, which may occur in various syndromes, including Noonan, Costello, tricho-dento-osseous syndrome, CHAND (curly hair, ankyloblepharon, and nail dystrophy) syndrome and lipoatrophic diabetes.

MONILETHRIX

A structural hair shaft abnormality caused by a lack of the medulla, which results in alternating elliptical nodes with intervening tapered non-medullated constrictions.

Aetiology

The thickness of the shaft varies because of the intermittent absence of the medulla; this gives rise to a beaded appearance. Depending on the degree of abnormality, the hair will break at the thin, non-medullated parts of the shaft and the affected individual may have quite short hair or indeed alopecia. It is usually inherited as an autosomal dominant with high penetrance but variable expressivity. It has been mapped to the keratin gene cluster on 12q11-q13 with mutations on the hair cortex keratin genes KRT86 and KRT 81.

Fig. 26.61 Pili annulati. There is a striking ringed appearance of spangly and shimmering alternating light and dark areas in the hair, caused by multiple air spaces in the cortex. (Courtesy of Dr David de Berker.)

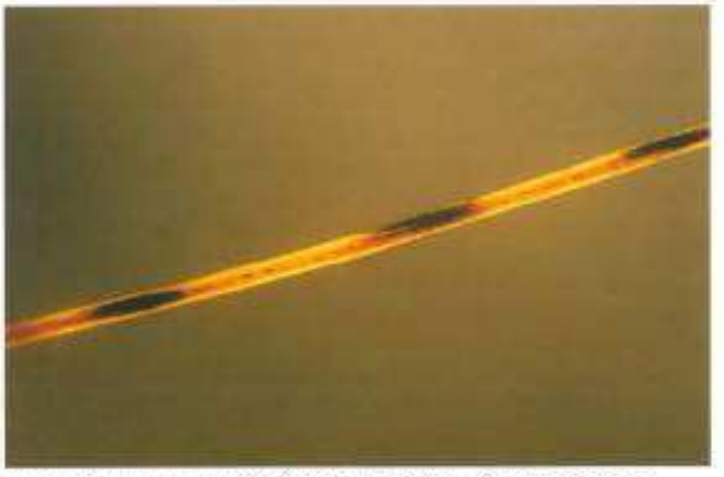


Fig. 26.62 Pili annulati. Alternating light and dark bands are visible under polarized light due to abnormal cavities in the hair shaft. (Courtesy of Dr David de Berker.)

Fig. 26.63 Uncombable hair syndrome. The hair is unmanageable and grows in a disorderly manner. It is often silver blonde in colour. (Courtesy of Dr Richard Staughton.)

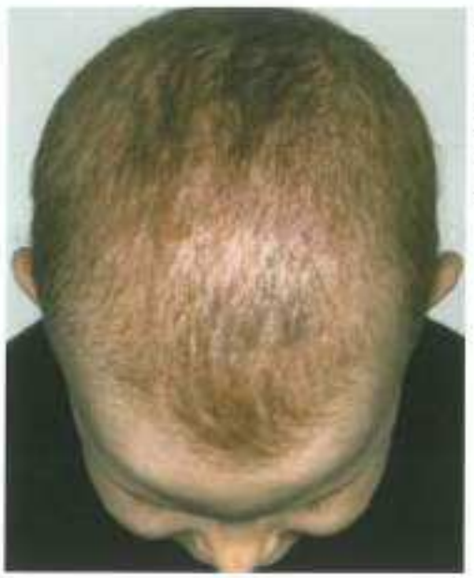


Fig. 26.64 Monilethrix. The back of the neck is particularly affected but the entire scalp may be involved. It is inherited as an autosomal dominant. There may be associated defects.

Clinical Features

Symptoms

Monilethrix usually begins in early childhood, particularly affecting the back of the scalp (Fig. 26.64), although the entire scalp and even the body hair may be affected. There is, however, considerable variation in the age of onset and degree of the disability.

Morphology

Brittle beaded hairs grow out of keratotic follicular papules (Fig. 26.65) and are rarely more than 1–2 cm in length. The hair breaks easily.

Systemic features

It may be associated with physical retardation, juvenile cataracts, syndactyly and nail and teeth abnormalities.

Management

The diagnosis is made by finding hairs with regular beading and no twisting under a light microscope (Fig. 26.66). There is no specific treatment. Although some patients make a complete recovery as they grow older, there is considerable individual variation.

PILI TORTI

A flattening of the hair shaft and a twisting through 180° on its own axis, which results in fragility of the hair and in alopecia.

Aetiology

There is a twisting of the hair shaft along its long axis, with usually about four or five twists at irregular intervals, giving it a spangled or beaded appearance. The hairs are brittle, break easily and do not grow to any length. The condition is usually inherited as an autosomal dominant disorder. It may occur as an isolated finding or sometimes in association with other abnormalities, including mental retardation. Pili torti has a number of clinical forms:

- hair only – classic in infancy affecting eyebrows, eyelashes and the entire scalp
- later onset – black unruly hair with mental deficiency
- with hearing loss (Björnstad) and additional hypogonadism (Crandall syndrome)
- with hypohidrotic ectodermal dysplasia
- with Menke's disease
- with Bazex syndrome (with basal cell carcinomas of the face and follicular atrophoderma).

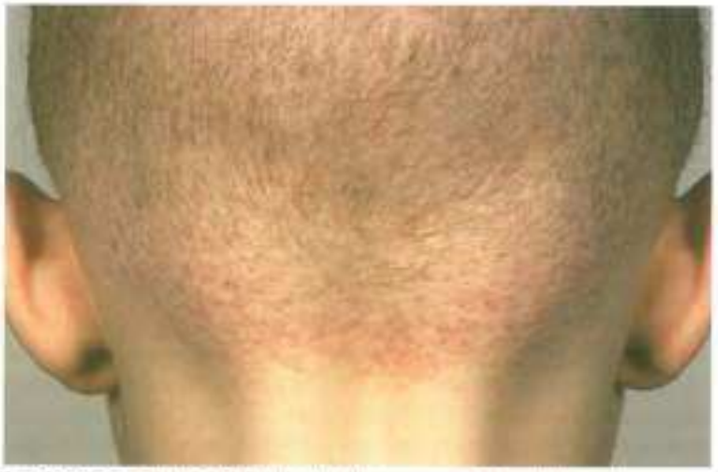


Fig. 26.65 Monilethrix. Brittle, beaded hairs grow out of keratotic papules, particularly at the back of the head. The hairs break easily and are short. It begins in childhood. There is keratosis pilaris elsewhere.

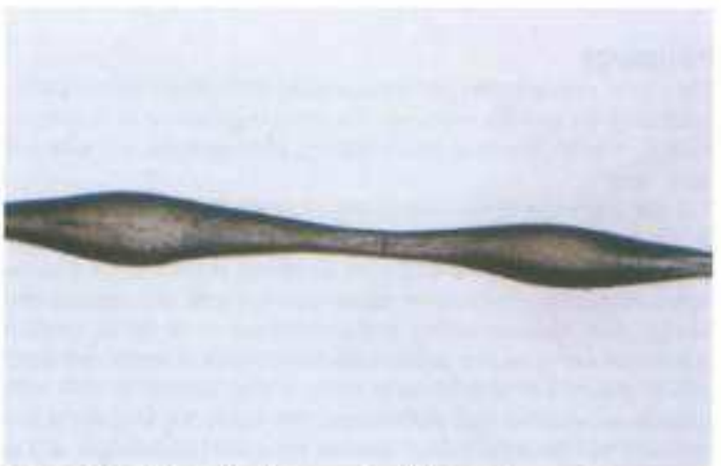


Fig. 26.66 Monilethrix. The thickness of the shaft varies because of the intermittent absence of the medulla, producing a beaded appearance of elliptical nodes with intervening non-medullated fragile constrictions.

Fig. 26.67 Pili torti. The affected hairs have a spangled appearance. The hair is fragile and patchy alopecia may result. All patients should be checked for deafness.

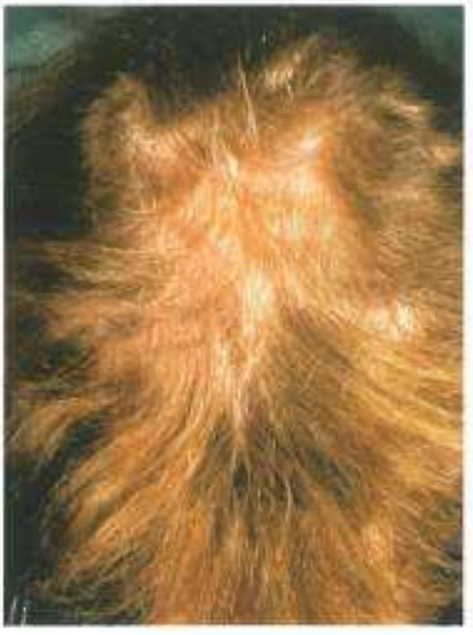


Fig. 26.68 Pili torti. There is hair loss because of the structural defect, usually beginning in early childhood. There is patchy alopecia and the hairs are different lengths.

Clinical Features

Symptoms

There is hair loss, usually beginning in early childhood.

Morphology

The hair is fragile and spangled (Fig. 26.67). There is a patchy alopecia and the hairs are different lengths (Fig. 26.68), some amounting to a coarse stubble and others achieving up to a few centimetres in length.

Distribution

The occipital and temporal regions are particularly affected but the eyebrows and eyelashes may also be involved.

Management

The typical appearance may be seen on light microscopic examination of a hair (Fig. 26.69). There is no specific treatment, although some patients do improve after puberty while others are permanently affected.

TRICHORRHEXIS NODOSA

A localized loss of cuticular cells, which permits the cortical cells to splay out forming nodes on the hair shaft.

Aetiology

The loss of cuticle results in frayed, cortical fibres that fracture readily, producing the nodular swellings. The most common cause is trauma, such as excessive brushing, back-combing, prolonged sun exposure and swimming.

It may also occur in association with trichothiodystrophy, Netherton's syndrome, Menke's disease, argininosuccinic acidaemia and citrullinemia.

Argininosuccinicaciduria results from an inborn absence of the enzyme argininosuccinase, which splits argininosuccinic acid into arginine and fumaric acid. Argininosuccinic acid accumulates in the blood, cerebral spinal fluid and urine. The arginine deficiency results in mental deficiency and weakened hair that fractures easily. It may present at birth with lethargy, seizures and respiratory distress (the infant may die), in the first year as mental retardation, developmental delay and hepatomegaly, and in early childhood as psychomotor retardation and CNS abnormalities. The hair is normal at birth, but becomes dry and dull. It responds to arginine supplements.

Citrullinemia results from a deficiency of the urea cycle enzyme, arginosuccinic acid synthetase, due to a genetic defect on 9q34. In infancy it causes similar clinical features to arginosuccinicaciduria with trichorrhexis nodosa, pili torti and sometimes the skin manifestations of acrodermatitis enteropathica.

Clinical Features

Symptoms

A patchy or diffuse alopecia.

Morphology

Small, grey-white nodules occur along the hair shaft. They particularly involve the distal portion of the hair shaft (split ends) due to mechanical trauma and weathering. They may also occur proximally (particularly in curly hair styled with chemicals and excess mechanical interference). Fracture of the hair shaft results.

Distribution

The scalp hair is normally affected (Fig. 26.70) but it may affect pubic or even body hair, eyebrows and eyelashes.

Management

The partial fractures of the hair shaft may be seen under the light microscope (Figs 26.71 and 26.72). If trauma is the cause, explanation and remedying the situation is all that is required.

TRICHOTHIODYSTROPHY

A disorder of brittle hairs caused by sulphur deficiency; it occurs as part of a neuroectodermal symptom complex.

Aetiology

It affects all body hair and is a mutation of a regulatory gene involved in the transcription of DNA. It is inherited as an autosomal recessive. It is known as the *BIDS syndrome* if associated with brittle hair, intellectual impairment, decreased fertility and short stature, *IBIDS* if ichthyosis is present, and *PIBIDS* if photosensitivity is a feature. In the latter, there may be reduced DNA repair due to instability or abnormal function of TFIIH (transcription factor IIH) as in some forms of xeroderma pigmentosum. The affected individuals have an unusual facial appearance.

Fig. 26.69 Pili torti. Twisting of the hair occurs at 180° along the long axis, resulting in fractures. (Courtesy of Dr R. P. R. Dawber.)

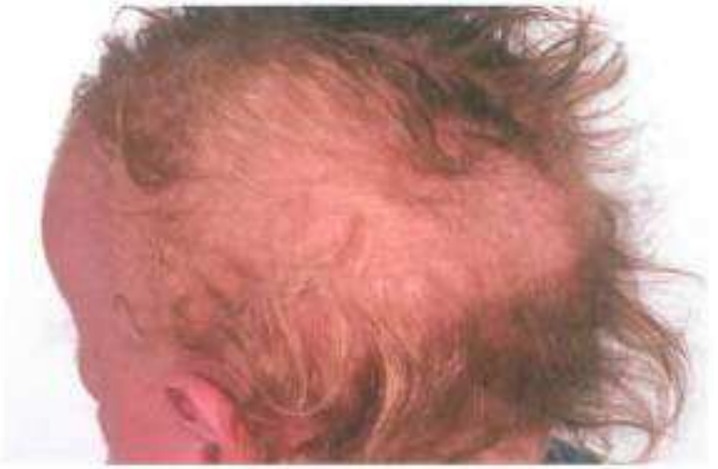
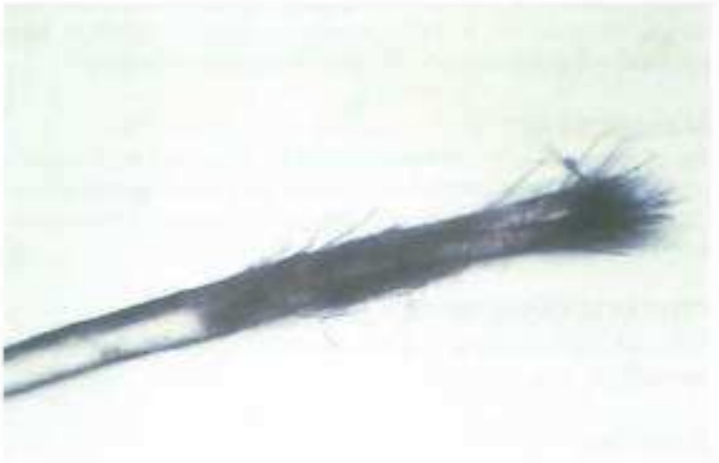
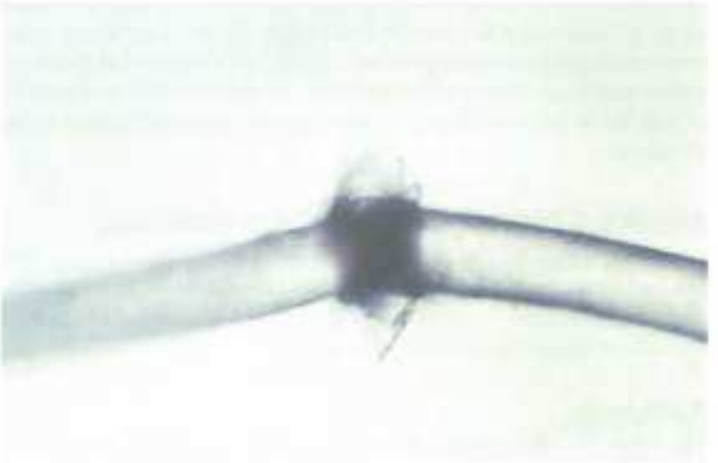


Fig. 26.70 Trichorrhexis nodosa. A patchy or diffuse alopecia results from fracture of the hair shaft as a result of localized loss of cuticular cells. In childhood, it may occur in certain inborn errors of metabolism.





Figs 26.71 and 26.72 Trichorrhexis nodosa. Frayed cortical fibres (Fig. 26.71) and small grey-white nodules (Fig. 26.72) simulating 'two paint brushes pushed together' occur as a result of loss of the cuticle, usually secondary to trauma.

A clean transverse fracture (trichoschisis) occurs in the hair shaft through both the cortex and the cuticle and there is a localized absence of cuticle cells. It occurs once the sulphur content is less than 50%.

Clinical Features

Symptoms

The hair is sparse, short, dry and coarse.

The ichthyosis may be of the lamellar type and the nails may be dystrophic. Mental and physical development is not always abnormal.

Morphology

The fragile hairs break near the skin surface and this is made worse by trauma. The degree of alopecia varies.

Distribution

The scalp (Fig. 26.73), eyebrows and eyelashes are affected, but other hairs may also be involved.

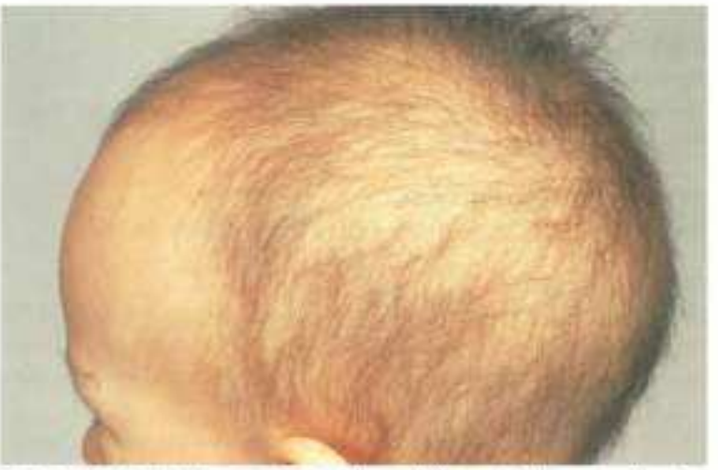


Fig. 26.73 Trichothiodystrophy. The hairs are brittle and fragile as a result of sulphur deficiency. They break near the surface, resulting in alopecia. Intellectual impairment, decreased fertility, short stature, photosensitivity and ichthyosis are other associated features.

Fig. 26.74 Trichostasis spinulosa. Multiple, vellus, unmedullated hairs arise from a single hair follicle, which is surrounded by a keratinized sheath at the surface, so giving a pigmented appearance.

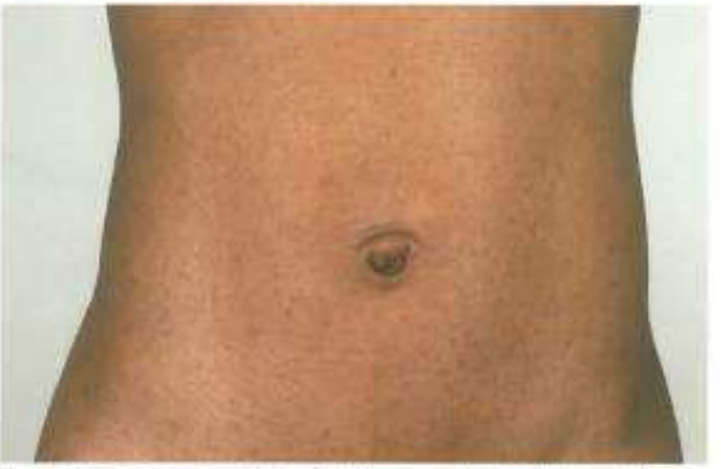


Fig. 26.75 Trichostasis spinulosa. The torso is predominantly involved. It presents in young adults. The skin feels rough.

Management

The trichoschisis can be seen as a band when the hair shaft is viewed under polarized light through the microscope. There is no effective treatment other than minimizing trauma. There is a prenatal test based on DNA repair measurements in trophoblast or amniotic cells and analysis of fetal hair at 20 weeks of gestation permits absolute confirmation of the diagnosis.

MENKE'S DISEASE (KINKY HAIR DISEASE)

A sex-linked recessive disorder associated with low serum copper and ceruloplasmin that results in abnormal and depigmented hair and skin, and progressive loss of milestones, neurological degeneration and mental retardation by the third month of infancy.

Aetiology

The condition affects male infants only and is inherited as a sex-linked recessive. There is a defect of copper absorption leading to decreased levels of copper in the blood, liver and hair. Pili torti and trichorrhexis nodosa are the hair abnormalities. Female heterozygotes may have pili torti. Some patients have additional aminoaciduria. There are mutations in ATP7A on Xq 13.3, which encodes a copper transporting ATPase and the diagnosis may be made prenatally.

Clinical Features

Symptoms

The hair is depigmented, sparse, brittle and twisted from infancy. It fractures easily, resulting in short hair.

Morphology and distribution

Pili torti, monilethrix and trichorrhexis nodosa of the scalp hair.

Systemic features

Infants appear normal for the first two or three months, but then fail to thrive, have seizures, become lethargic, hypotonic, hypothermic, anaemic and mentally retarded. There is a characteristic facies of pudgy lips, cupid's bow of the upper lip and horizontal eyebrows. The skin colour is diluted, because tyrosinase is a copper-dependent enzyme. In addition there may be vascular anomalies, including aneurysms, bladder diverticula, joint laxity and soft doughy skin due to connective tissue involvement.

Management

The prognosis is poor and most untreated children are dead within a couple of years. Early parenteral copper therapy may be helpful in combating the defect in intestinal copper transport that leads to the low serum and tissue copper.

TRICHOSTASIS SPINULOSA

The production of multiple, vellus, unmedullated hairs from a single hair follicle.

Aetiology

Trichostasis spinulosa is a relatively common condition of young adults in which multiple hairs occur in one follicular canal. It also occurs in the elderly, when it may be a normal age-related abnormality in which telogen hairs are retained in the pilosebaceous follicles.

Clinical Features

Symptoms

Pigmented goosebumps.

Morphology

Multiple vellus hairs may be visible escaping from a single hair follicle that is surrounded by a keratinous sheath (Fig. 26.74).

Distribution

Shoulders, back, arms, front of the chest and abdomen (Fig. 26.75). In the elderly may also occur on the nose and face.

Management

The condition may respond to depilatory waxes or topical retinoic acid

Disorders of pigmentation 27

In the skin, melanocytes are present in the basal cell layer of the epidermis and are responsible for producing the pigment known as melanin. They occur in a ratio of approximately one melanocyte to five basal cells. Since they do not stain with haematoxylin and eosin, they appear as clear cells in routine sections. They also occur in the uveal tract (choroid, ciliary body and iris), leptomeninges, inner ear (cochlea) and mesentery. Special stains are required to appreciate the highly dendritic quality of the melanocyte. The Fontana–Masson stain depends upon the reduction of silver nitrate to free silver by melanin and can be used on formalin-fixed tissue. The DOPA (3,4-dihydroxyphenylalanine) stain, however, has to be done on fresh tissue and depends on the oxidization by tyrosinase of DOPA to dopamelanin, which is black.

Each melanocyte supplies pigment to many keratinocytes and this association is known as the epidermal melanin unit. The keratinocytes phagocytose the melanin-laden dendritic tips of the melanocyte and, therefore, the pigmentation of an individual skin depends primarily on the amount of melanin transferred to the keratinocyte. Melanocytes contain melanosomes in their cytoplasm. The melanosomes contain tyrosinase and various proteins. There are four stages of development of melansomes, stages I to IV, as they pass from the perinuclear area of the melanocyte to the dendrites. In black skin, the predominant form of melanosome is stage IV.

Melanocytes are derived from melanoblasts, which migrate from the neural crest (an ectodermal structure) during fetal development via the mesenchyme to the epidermis and hair follicles. They disappear from the dermis by the end of gestation except on the head and neck, dorsa of the distal extremities and the sacrum (site of the Mongolian blue spot). These are the sites where blue naevi occur. If melanoblasts fail to migrate from the neural crest or fail to differentiate into melanocytes, a condition known as *piebaldism* (white forelock of hair with white patches on the skin) results. There are possibly two populations of these cells. Those in the interfollicular epidermis are more sensitive to autoantibodies and those in the hair follicles, which are less so and this is where repigmentation is more likely in vitiligo.

The same number of melanocytes are present in both white and black skin but the numbers of melanocytes actively synthesizing melanin and of stage IV melanosomes are increased in the latter. Melanosomes are pigment-containing, electron-dense granules produced within the melanocyte during the process of manufacturing melanin (melanogenesis). These melanin granules partially surround the nucleus of the keratinocyte and protect it from ultraviolet light, such that five times less ultraviolet light reaches the papillary dermis in black than in white skin. Each melanocyte serves several keratinocytes.

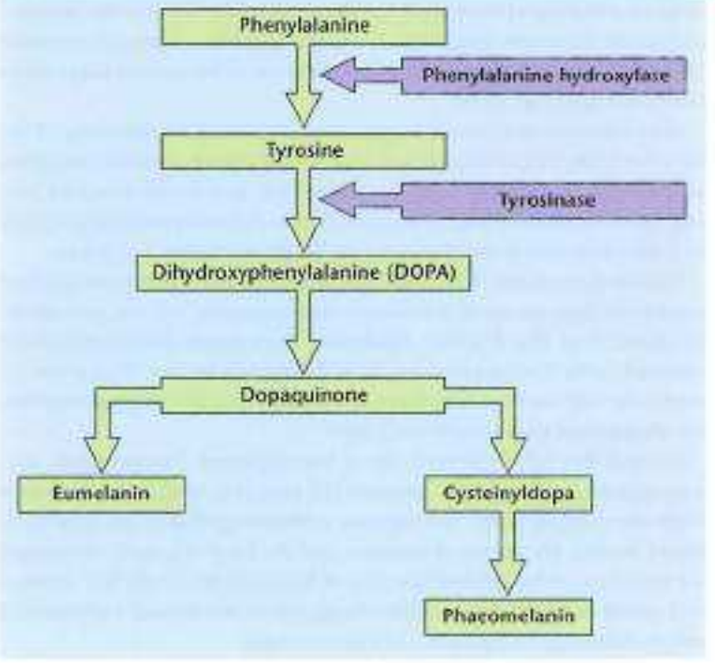
Melanosomes are members of the lysosomal-related organelle family, which include platelet dense granules, lytic granules of cytotoxic lymphocytes and NK cells. Genetic disorders of these organelles are responsible for the Hermansky–Pudlak and Chediak–Higashi syndromes. Melanosome abnormalities also may occur with giant melanosomes in the café-au-lait patches of neurofibromatosis and in certain birth marks, such as naevus spilus. Melanocytes are largely protective against ultraviolet irradiation. Every individual has a constitutional amount of melanin that is capable of increasing either as a result of ultraviolet irradiation or under the influence of increased production of certain hormones, in particular melanocyte-stimulating hormone (MSH) and adrenocorticotrophic hormone (ACTH).

There are three forms of MSH, known as α-, β- and γ-melanotrophins. They are small peptide hormones that are derived from the same precursor peptide pro-opiomelanocortin from which ACTH, corticotrophin-like intermediate-low peptide, β-lipotrophin and β-endorphin are also derived. ACTH comes from the anterior lobe of the pituitary gland and α-MSH is derived from ACTH in the intermediate lobe.

Melanin is derived from phenylalanine via intermediates, a reaction that is under the control of the enzyme tyrosinase. If the reaction is continued and melanin is oxidized, a colourless compound results. This is how hydrogen peroxide or intense ultraviolet light irradiation bleaches the hair. Hair is red because of the presence of phaeomelanin, which is formed from dopaquinone via a reaction with cysteine.

The steps in the production of melanin are illustrated in Table 27.1. If the enzyme phenylalanine hydroxylase is deficient, tyrosine is not formed and phenylalanine accumulates, which leads to *phenylketonuria*, a condition of blue eyes, fair skin and blonde hair, owing to impaired melanin synthesis, and of behavioural irregularities, epilepsy, extrapyramidal signs and mental retardation if the disorder is not promptly treated by a low-phenylalanine diet. Eczema, sclerodermatous changes and pyogenic infections are frequent. It is diagnosed by the routine testing of the urine of all neonates for phenylpyruvic and phenylacetic acids, which impart a musty odour (as does the sweat) and the Guthrie heel prick blood test.

TABLE 27.1 The production of melanin



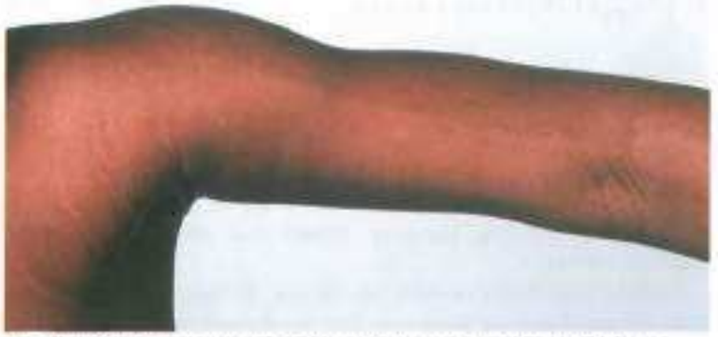


Fig. 27.1 Voigt's lines. There is a sharply demarcated line of transition from darker to lighter skin at the anterolateral junction of the upper arms. It is quite normal in black skin.

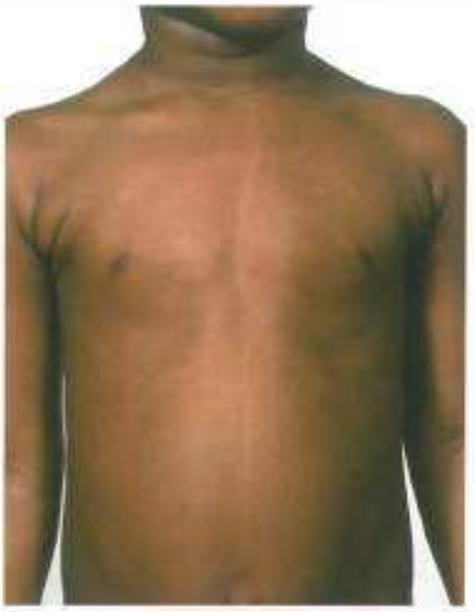


Fig. 27.2 Midline hypopigmentation. A band of hypopigmentation over the mid-sternum, which may extend upwards or downwards, is a common normal variant in black skin.

It is inherited as an autosomal recessive and is one of the commonest inborn errors of metabolism. It is virtually eradicated in the West because of blood or urine testing at birth. It is treated by restricting the dietary intake of phenylalanine with tyrosine and other amino acid supplements. If tyrosinase is absent or non-functioning, *albinism* results, with varying degrees of white skin, blonde hair and photophobia. Squamous cell carcinoma is common in albinos, particularly those living in sunny climates.

Melanocytes may malfunction as a result of certain pathological states. For example, they may proliferate in a benign manner under the influence of ultraviolet light, as in solar lentigines or in certain genetic disorders such as the Peutz–Jegher syndrome, a condition of pigmented macules of the mouth and extremities associated with intestinal polyps. They may proliferate in a malignant manner in malignant melanoma. Melanocytes may be destroyed as part of an autoimmune process, as in vitiligo, or following inflammatory conditions that disrupt the basal layer of the epidermis, such as lichen planus and discoid lupus erythematosus.

Variations in skin colour occur quite normally in black skin, for example Voigt's (or Futcher's) lines at the transition from the flexor to the extensor surface on the upper arms (Fig. 27.1) and a midline hypopigmentation (Fig. 27.2) on the anterior chest. Pigmentation of the palmar skin creases is also normal (Fig. 27.3).

After exposure to ultraviolet light, there is immediate darkening of the skin that fades within 6 to 8 hours. This is probably the result of oxidation of pre-existing melanin or its precursors but not the synthesis of new pigment. Delayed tanning is the result of new pigment production, caused by both ultraviolet A and B and is usually apparent after 2 or 3 days.

Examination of the skin under the Wood's light, which is an artificial ultraviolet light source of wavelength approximately 365 nm, reveals the localization of the disorder. Epidermal pigmentary abnormalities are detected under the light whereas dermal disorders are not. Thus pityriasis versicolor and freckles, which are epidermal disorders of pigmentation, are accentuated under the Wood's light.

Normal skin colour is made up of four pigments: haemoglobin, oxyhaemoglobin, melanin and carotene. The pink skin of a Caucasian results from the visibility of the red pigment oxyhaemoglobin in the superficial blood vessels. The pallor of anaemia and the blue or purple of cyanosis are functions of diminished amounts of haemoglobin in the first instance and of reduced (deoxygenated) haemoglobin in the second. Carotene is a yellow substance found in the subcutaneous fat.

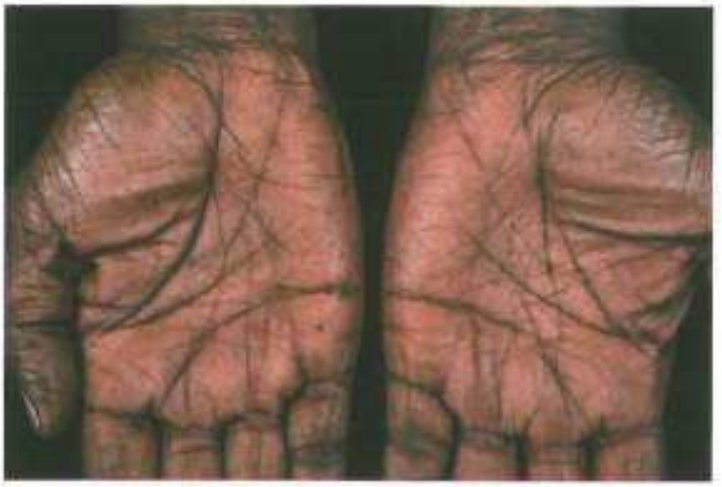


Fig. 27.3 Racial palmar skin crease pigmentation. Pigmentation of the skin creases is pathological in Caucasians, but not in dark-skinned races.

Generalized diffuse hyperpigmentation

Apart from the genetic and sun-induced causes of hyperpigmentation, there are several important pathological causes.

Hormonal Causes

The first presenting feature of Addison's disease may be a gradual increase in pigmentation of the skin (Figs 27.4 and 27.5). This is particularly obvious in the skin creases of the palms (Fig. 27.6) and soles, in the flexures, in scars, along the nails and on the buccal mucous membranes: conjunctivae, vagina and gums. The patient may also note a failure to lose a summer tan in the winter months. The condition is caused by increased production of MSH and ACTH in response to hypoadrenalism. A similar hyperpigmentation occurs in *Cushing's syndrome* caused by a basophil adenoma of the pituitary or an ectopic source of ACTH. A very striking hyperpigmentation occurs in *Nelson's syndrome*, which arises after bilateral

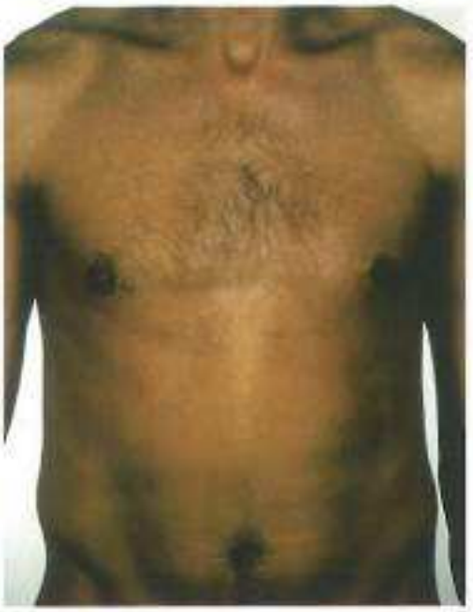


Fig. 27.4 Addison's disease.
The cause of generalized hyperpigmentation must be investigated. This patient was suffering from Addisonian adrenal failure and his anterior pituitary was overproducing ACTH and MSH.

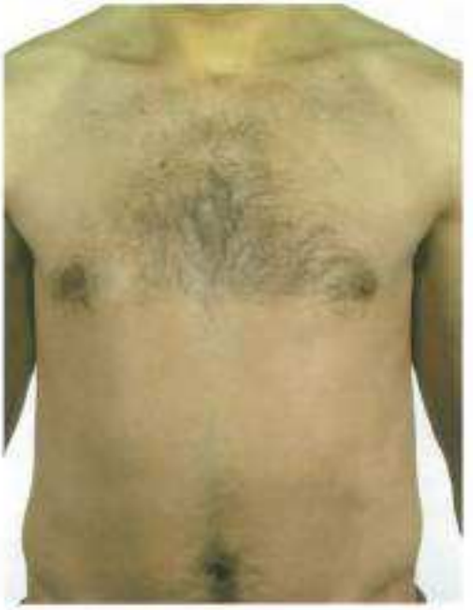


Fig. 27.5 Treated Addison's disease.
The skin colour (Fig. 27.4) returned to normal with steroid replacement.

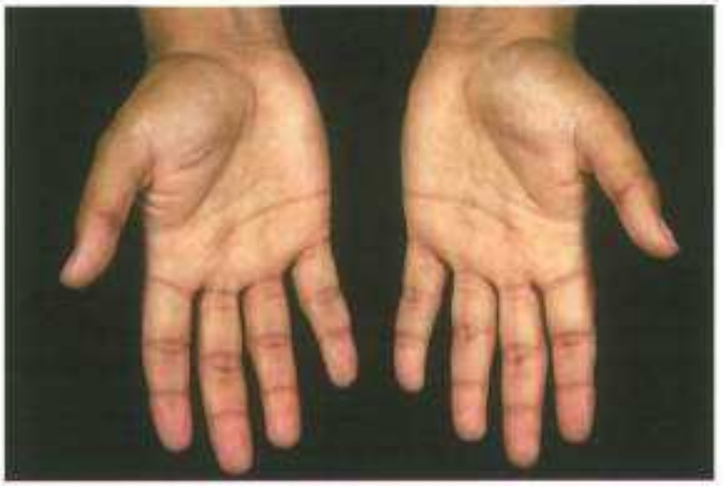


Fig. 27.6 Addison's disease. There is general hyperpigmentation and in particular the palmar skin creases are hyperpigmented. (Courtesy of Prof. A. McGregor.)

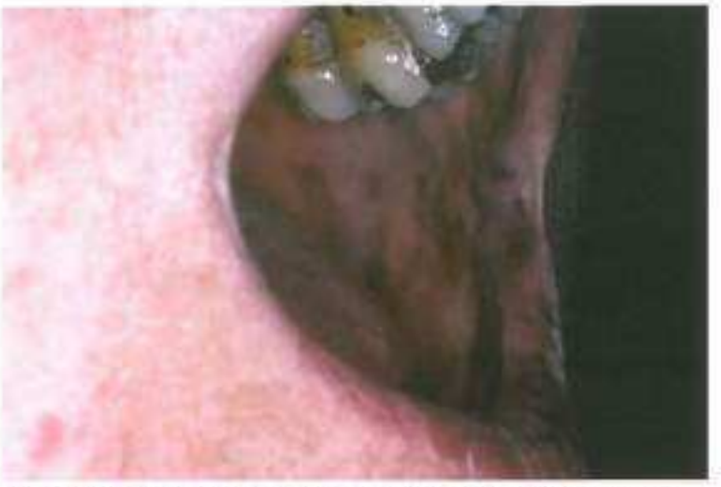


Fig. 27.7 Laugier–Hunziker syndrome. Pigmentation occurs on the buccal mucosae in Addison's and disappears with treatment. Laugier-Hunziker syndrome is Addisonian non-racial hyperpigmentation with normal adrenal function.

adrenalectomy for adrenal hyperplasia, when pituitary peptide production from a functioning chromophobe tumour is completely unopposed. A pigmentary anomaly identical to that of Addison's disease occurs in the *Laugier–Hunziker syndrome* (Fig. 27.7) but there are no systemic manifestations. Hyperpigmentation is also seen in thyrotoxicosis and chronic renal failure secondary to increased circulating levels of MSH, which is normally degraded by the kidney. Oestrogens also appear to have some effect on melanogenesis and generalized hyperpigmentation is often noticed in pregnancy, particularly of the nipples, linea alba, axillae and genitalia.

Metabolic Causes

Hyperpigmentation is seen in any patient with wasting or cachexia, for example caused by overwhelming tuberculosis, carcinomatosis or malabsorption. Nutritional disorders, in particular vitamin B_{12} deficiency, can produce hyperpigmentation. Hyperpigmentation, particularly in sun-exposed areas, occurs in scleroderma (Fig. 27.8), porphyria cutanea tarda

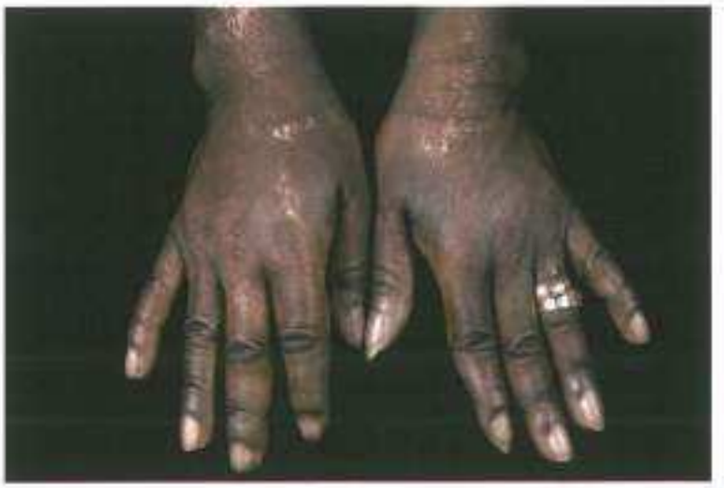


Fig. 27.8 Scleroderma. This lady's skin was getting darker and her holiday sun tan did not fade. The vitiligo suggested an autoimmune process and her hands were sclerodermatous and fingers sausage-like. The synacthen test was normal.

Fig. 27.9 Porphyria cutanea tarda. Hyperpigmentation may occur in solar-exposed areas. Considerable solar elastosis has also resulted in furrowing of the skin.

(Fig. 27.9) and primary biliary cirrhosis (Fig. 27.10). A striking pigmentation occurs in most patients with *haemochromatosis* (Ch. 22), a disorder of iron metabolism that leads to cirrhosis and diabetes mellitus. The pigmentation may be brown-black, bronze or blue-grey and the distribution is similar to that in Addison's disease with accentuation in the sun-exposed areas. The different shades result from a combination of melanin deposition and haemosiderin. It often precedes other manifestations of the disease.

Drug Causes

Many drugs have been recorded as producing pigmentation (Ch. 18), including cytotoxics (cyclophosphamide, bleomycin and 5-fluorouracil), clofazimine and zidovudine (Ch. 14). Chloropromazine causes a slate-grey discoloration probably through a metabolite that binds to melanin, although more commonly it produces hyperpigmentation secondary to its phototoxic effects. A number of drugs act in this way. Busulphan produces a similar pigmentation to that seen in Addison's disease. Arsenic induces a raindrop pigmentation. Mercury causes a slate-grey pigmentation, especially of the skin folds and lead is deposited in the nails and gingival margin (the so-called lead line). Amiodarone also produces a slate-grey discoloration. Minocycline can produce a striking focal blue discoloration in the skin and mucous membranes (Ch. 18). Topical nitrogen mustard induces hyperpigmentation. Argyria (Fig. 27.11) secondary to chronic ingestion of silver produces a blue-grey discoloration of the skin, particularly in the sun-exposed areas, through the deposition of silver.

Localized hyperpigmentation

MELASMA (CHLOASMA)

A patchy increased pigmentation of the face mainly in women, often precipitated by pregnancy or oral contraceptives and exacerbated by sunlight.

Aetiology

The condition is common. Many women develop it while pregnant and for the majority the condition fades after delivery. Some acquire it while taking oral contraceptives, but it does not always go away on stopping them. All sufferers find that it is increased with exposure to ultraviolet light, and in those for whom there is no obvious hormonal explanation it may be the final result of years of sun exposure. It is not confined to women and indeed is common in Mediterranean, Middle Eastern and Asian men but not in Anglo-Saxon men who do not tan easily. Almost certainly, excess ultraviolet irradiation is the most important factor in affected males. MSH levels are quite normal in patients with melasma.

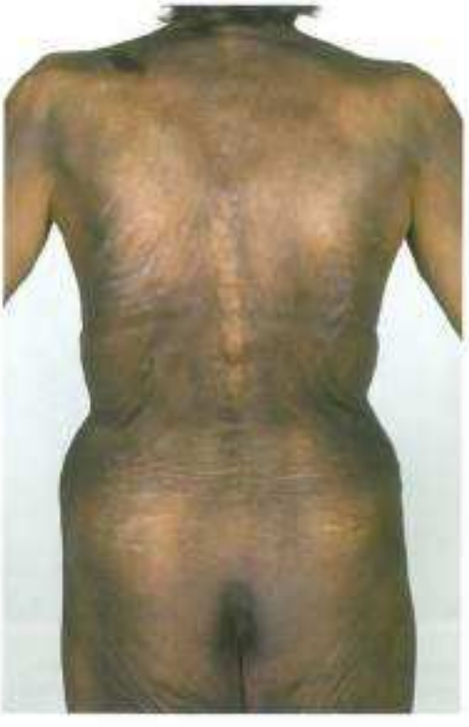


Fig. 27.10 Primary biliary cirrhosis. The classic dermatological presentation of primary biliary cirrhosis is generalized pruritus but patients frequently become hyperpigmented.

Fig. 27.11 Argyria. Many drugs cause pigmentation of the skin, nails and/or mucous membranes. This man was a silversmith and unwittingly ingested large amounts of silver.

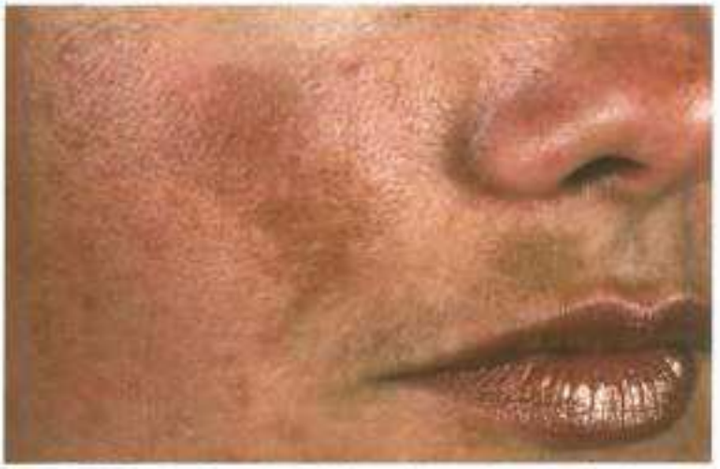


Fig. 27.12 Melasma. There is a patchy hyperpigmentation on the cheeks and upper lip. Although it may be precipitated by pregnancy or oral contraceptives, sunlight makes it worse.

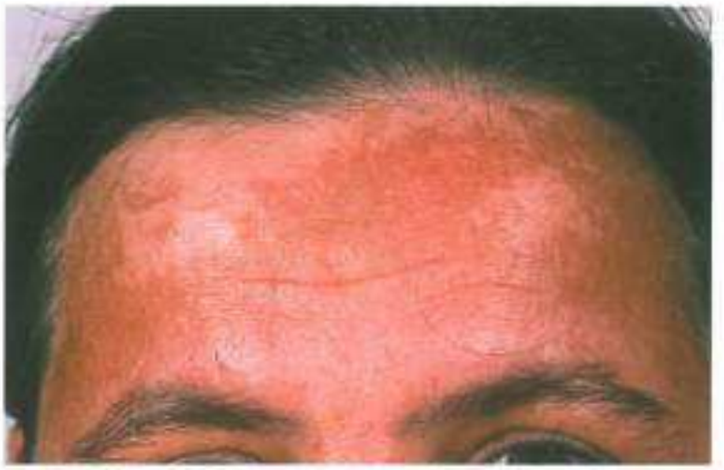


Fig. 27.13 Melasma. There is a patchy brown pigmentation on the forehead. Initially it disappears in the winter to return in the summer if the significance of sun exposure is not appreciated.

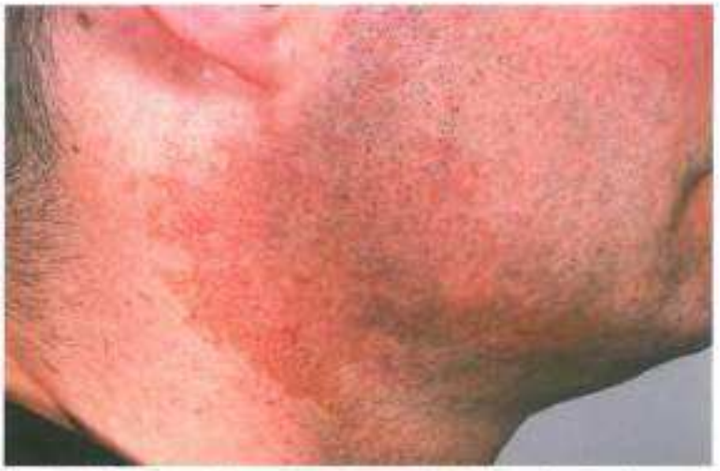


Fig. 27.14 Melasma. It does occur in men particularly if they have lived in a sunny climate. This serves to emphasize the importance of ultraviolet irradiation in its aetiology.

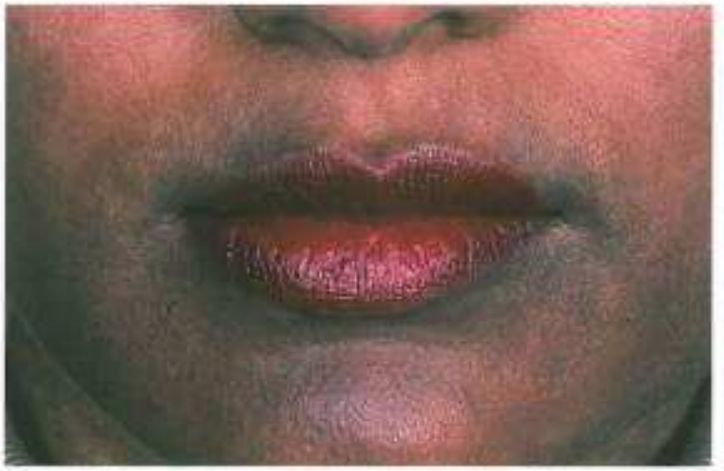


Fig. 27.15 Erythrose péribuccale pigmentaire de Brocq. There is pigmentation symmetrically distributed around the mouth. It is probably due to a photodynamic substance in poorly manufactured cosmetics.

Clinical Features

Symptoms

Pigmentation on the face.

Morphology

The pigmentation is patchy, ill defined and light brown or darker depending on recent solar exposure.

Distribution

It is usually fairly symmetrical on the cheeks (Fig. 27.12), forehead (Fig. 27.13), over the nose, on the upper lip (often simulating a moustache), chin and neck (Fig. 27.14).

Management

Explanation and solar protection are most important as the condition is difficult to treat at present. Fair-skinned individuals have the best prognosis and many recover completely after pregnancy or stopping the contraceptive pill. They must, however, be advised to use a sunscreen on the face in the sun to ensure that the pigmentation does not return and remain indefinitely. In darker-skinned individuals, the condition can be remarkably persistent. They too should be advised to protect the skin obsessionally with high-protection sunscreens which block both ultraviolet A and B. 2–4% hydroquinone in combination with 0.05% retinoic acid and 1% hydrocortisone may be beneficial. In higher concentrations, hydroquinone results in erythema. Wood's light examination is important. Epidermal (increased melanin in the basal and suprabasal layers) melasma (brown) is accentuated and may respond to treatment. Dermal melasma (blue-grey) is not and does not respond well to treatment.

The differential diagnosis is *Riehl's melanosis* or *erythrose péribuccale pigmentaire de Brocq* (Fig. 27.15). Both are thought to be due to a photodynamic substance in cosmetics. The former may be extensive on the face and even neck and chest and is a brown-grey colour. Histologically, there is pigmentary incontinence, liquefaction, degeneration and a band-like lichenoid pigmentation. The latter is more or less symmetrical around the mouth, but spares a narrow perioral ring. Both are rarely seen, possibly because the manufacturing of cosmetics is more sophisticated than it was.

EXOGENOUS OCHRONOSIS

A hyperpigmentation with papules on the face and elsewhere secondary to the prolonged use of hydroquinone-containing skin-lightening creams.

Aetiology

Localized ochronosis has become commonplace amongst Africans who use high concentrations (6–8%) of hydroquinone to lighten the skin. A hyperpigmentation occurs on prominent parts of the face about 6 months later. Occasionally ochronosis of the cartilage of the ear occurs.

The fact that catechols and phenols such as hydroquinone and monobenzylether of hydroquinone can cause loss of pigment was first noted in factory workers who wore gloves made of rubber containing monobenzylether of hydroquinone as an antioxidant. Pigmentary changes have also been described in patients exposed to phenol-containing germicides, hydroquinone photographic developer and various rubber products treated with monobenzylether of hydroquinone. These compounds are very similar chemically to melanin precursors and have similar effects on pigment cells. Topical mercury and resorcinol can produce the same effects.

Hydroquinone has, therefore, been used topically to treat various disorders of hypermelanosis. Monobenzylether of hydroquinone causes permanent depigmentation and may affect areas remote from the site of application. It is reserved for the very occasional patient with widespread vitiligo who wishes to be completely depigmented. Contact sensitization is common.

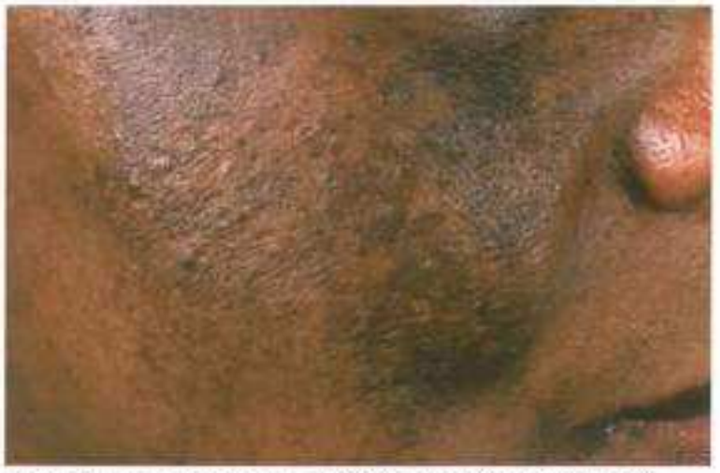


Fig. 27.16 Localized ochronosis. Localized hyperpigmentation over bony prominences, such as the cheeks, occurs secondary to the use of skin-lightening creams that contain hydroquinone.

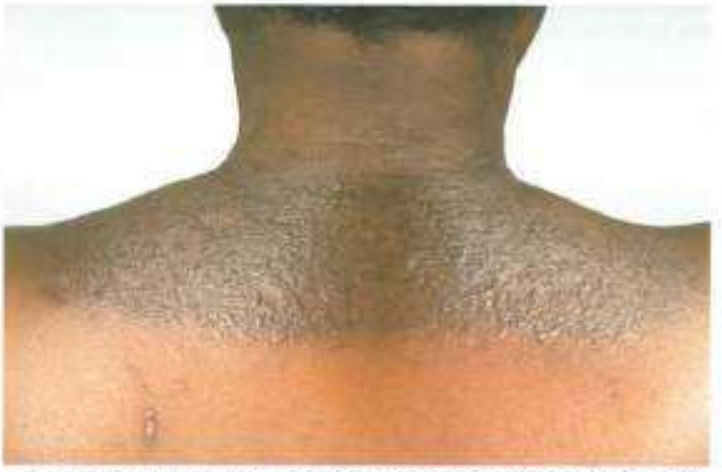


Fig. 27.17 Ochronosis. A papulo-nodular pigmentation occurs over the back of the neck that is quite well delineated. Ultraviolet light may be an additional factor.

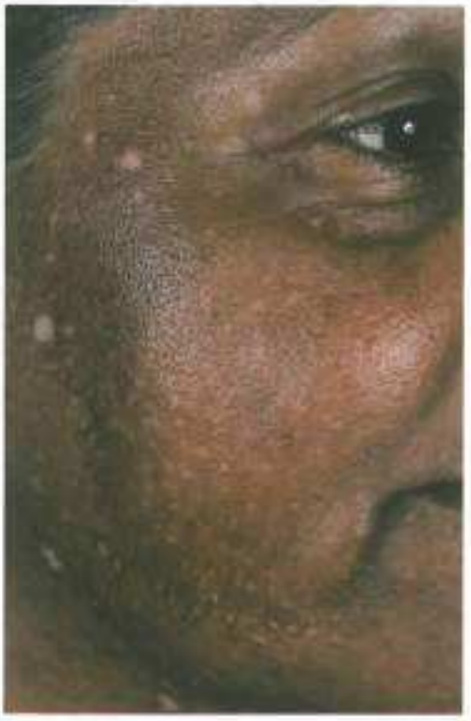


Fig. 27.18 Depigmentation secondary to hydroquinone. Confetti-like depigmentation may occur after the prolonged use of higher concentrations of hydroquinone to 'bleach' the skin.

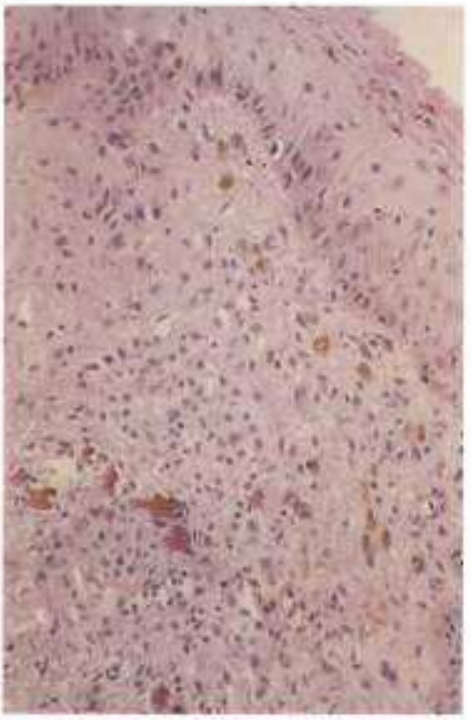


Fig. 27.19 Ochronosis. Swollen irregular golden brown ochronotic collagen fibres are visible in the dermis.

Hydroquinone has effects that are limited to the site of application: the resulting hypopigmentation is neither complete nor usually irreversible and, therefore, it is used in low concentrations to treat various disorders such as melasma, lentigines and postinflammatory hyperpigmentation. It is most useful if the pigment is in the epidermis: this can be determined under Wood's light examination where the pigment will be more obvious. If the pigment is in the dermis, it will be less obvious and this type of hyperpigmentation does not respond well to hydroquinone. In doses higher than 2%, exogenous ochronosis and contact dermatitis may occur.

Clinical Features

Symptoms

A disfiguring pigmentation.

Morphology

After initial erythema, a macular pigmentation results that gradually becomes darker with the formation of caviar-like papules (Fig. 27.16). The skin between the papules is often quite normal when stretched. A papulo-nodular stage may follow (Fig. 27.17), which may be annular and granulomatous. A confetti-like (Fig. 27.18) hypopigmentation may ensue.

Distribution

The face (particularly over bony prominences such as the cheeks and lateral to the eyes) is affected as can be the back of the neck.

Management

A skin biopsy is helpful because the ochronotic collagen fibres may be demonstrated in the dermis (Fig. 27.19) and these may be surrounded by a granulomatous reaction. The pigmentation shows little tendency to fade and patients often revert to using the preparation again. Use of 0.05% retinoic acid and a sunscreen is recommended. Dermabrasion and the CO_2 laser have been tried.

GENERALIZED OCHRONOSIS (ALKAPTONURIA)

An inborn error of homogentisic acid metabolism resulting in a triad of black discoloration of the urine with subsequent renal tract calculi, arthropathy and ochronosis.

Aetiology

Generalized ochronosis is a rare inborn error of metabolism with the defect localized to chromosome 3q 21-23 giving rise to renal or hepatic deficiency in the enzyme homogentisic acid oxidase. This, in turn, leads to excessive levels of homogentisic acid, which is oxidized and polymerized by the enzyme polyphenol oxidase, which is present in skin and cartilage, to benzoquinone acetic acid, a melanin-like product that binds irreversibly to collagen. This can be seen in connective tissues, cartilage and skin. The disorder is inherited as an autosomal recessive. It may also occur secondary to certain drugs (for example phenol and mepacrine, which inhibit sulphydryl groups in the enzyme).

Clinical Features

Symptoms

A distinctive cutaneous pigmentation.

Morphology

The pigmentation is of blue or blue-grey colour and is most visible when the skin overlying cartilage or tendons is thin or atrophic secondary to sun damage.

Distribution

The pinnae (Fig. 27.20), tip of the nose, costochondral junctions and extensor tendons of the hands are affected. Since the pigment is excreted in sweat, those areas well-supplied with sweat glands, such as the axillae (often the earliest sign in adolescence) and genital areas, may become pigmented and the underclothing may be stained.

Systemic features

Pigment is deposited in the sclera (Osler's sign), which does not affect vision. Deposition in the wax (causing it to be darker than normal), tympanic membranes and ossicles may diminish hearing and cause tinnitus.

Black discoloration of the urine may or may not be noticed as a dark or pink staining of the diapers in infancy. Urinary calculi develop eventually. Because of the efficient renal excretion of homogentisic acid, the arthropathy appears later in the third or fourth decade and is made worse by the deterioration in renal function as years go by. There is marked deposition in pigmentation in articular surfaces and synovia, which include the cartilages and intervertebral discs of the spine (with sparing of the bones); this leads to fractures, ankylosis and often crippling arthritis of large weight-bearing joints such as the knees, but the hands and feet are uninvolved. The cardiovascular system may be affected in 50% of those with the disorder, with valvular pigmentary deposits and calcification leading in particular to aortic stenosis.

Management

There is no specific treatment for alkaptonuria. A low phenylalanine and tyrosine diet does not alter the course of the disease. Nitisinone (an inhibitor of homogentisic acid) and long-term ascorbic acid (reduces homogentisic acid excretion) may be of benefit. Urinary and serum homogentisic acid may be measured by spectrophotometry. Histologically, yellow-brown, crescentic masses are deposited within swollen collagen fibres with solar elastosis.

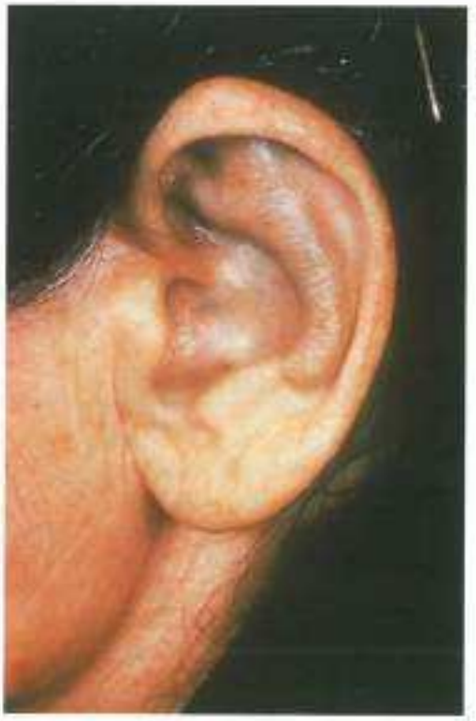


Fig. 27.20 Alkaptonuria. Blue-grey pigmentation is visible over the pinna. (Courtesy of St Mary's Hospital.)

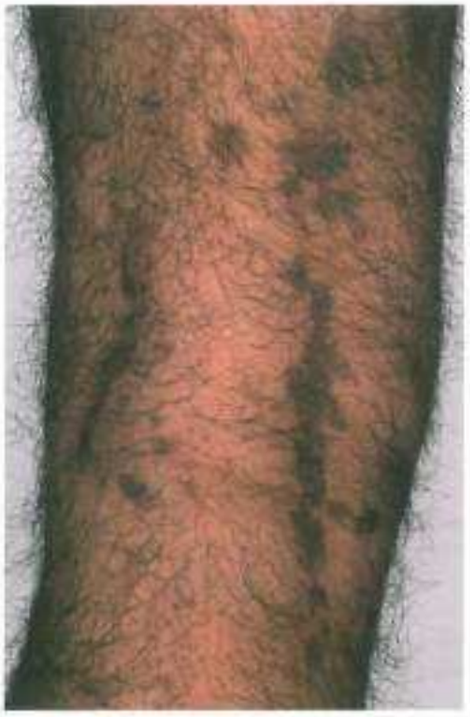


Fig. 27.21 Lichen planus. This always results in postinflammatory hyperpigmentation whatever the racial background. The intense lymphohistiocytic infiltration of the upper dermis damages the basement membrane and leads to pigmentary incontinence. The diagnosis is made from the distribution of the lesions.

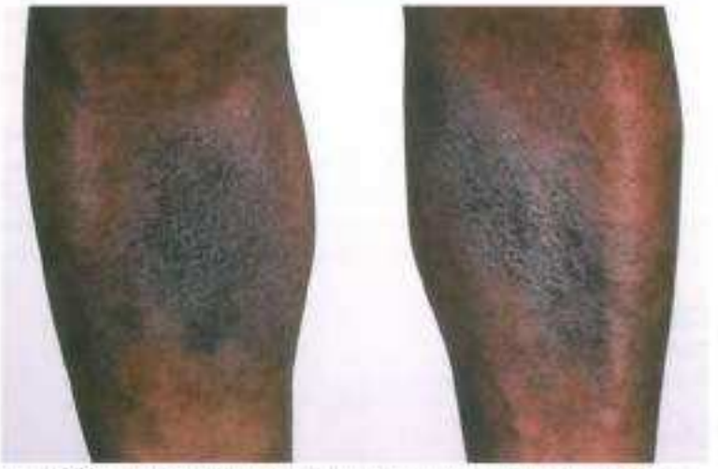


Fig. 27.22 Lichen simplex causing postinflammatory hyperpigmentation. Lichen simplex is a form of eczema and this is still visible but postinflammatory pigmentation has already occurred.

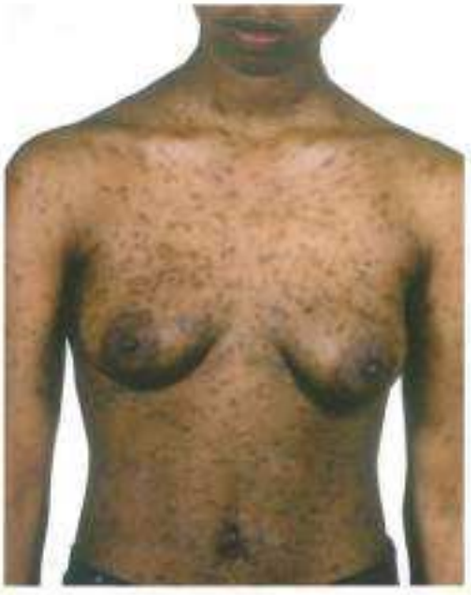


Fig. 27.23 Pityriasis rosea. Postinflammatory pigmentation is a problem that follows any inflammatory disorder in a black skin. Here pityriasis rosea is the cause (note the symmetrical oval patches on the torso), but such pigmentation would not follow in a white skin.

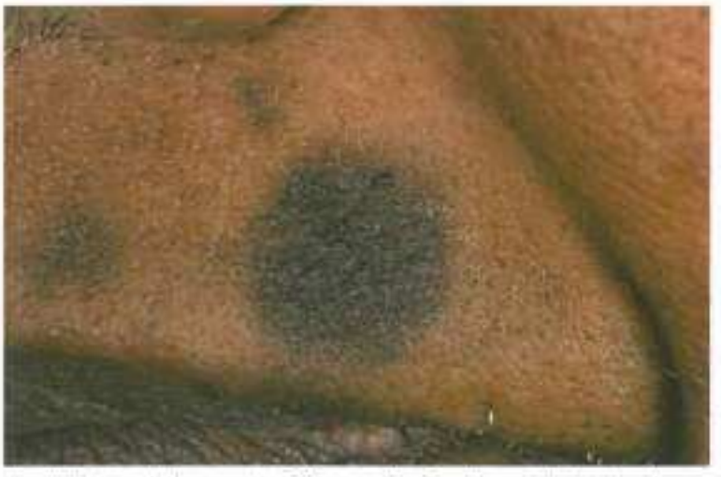


Fig. 27.24 Fixed drug eruption. The round configuration and the history of erythema and swelling that occur each time the patient ingested a laxative containing phenolphthalein suggested the diagnosis.

Postinflammatory hyperpigmentation

Hyperpigmentation may follow any skin disease but particularly those that affect the basal cell layer of the epidermis and result in pigmentary incontinence, e.g. lichen planus (Fig. 27.21) and lupus erythematosus. Other inflammatory diseases, such as acne, pityriasis rosea or eczema, barely produce any discernible pigmentation in the Caucasian but may produce long-lasting hyperpigmentation in dark skins. Although macrophages eventually clear it, the pigmentary changes are untreatable, so it is necessary to prevent the inflammation as much as possible, by treating the initial condition effectively.

Common causes are acne, eczema (Fig. 27.22), pityriasis rosea (Fig. 27.23), fixed drug eruption (Fig. 27.24), phytophotodermatitis, Berloque dermatitis (Fig. 27.25), lichen planus and its variants and discoid lupus erythematosus.

If changes in addition to pigmentation are present, for example scaling (Fig. 27.26), the condition is still active and is, by definition, not postinflammatory hyperpigmentation. Three disorders are described here that are sufficiently specific to merit separate discussion.

RETICULATED PIGMENTED ANOMALY OF THE FLEXURES

A syndrome characterized by a reticulate macular hyperpigmentation predominantly in the flexures.

Aetiology

The disorder starts in adolescence or early adult life. There is a loss of function in KRT 5 (which maintains the integrity of the basal keratinocytes) located in 17p13.3 and is inherited as an autosomal dominant.

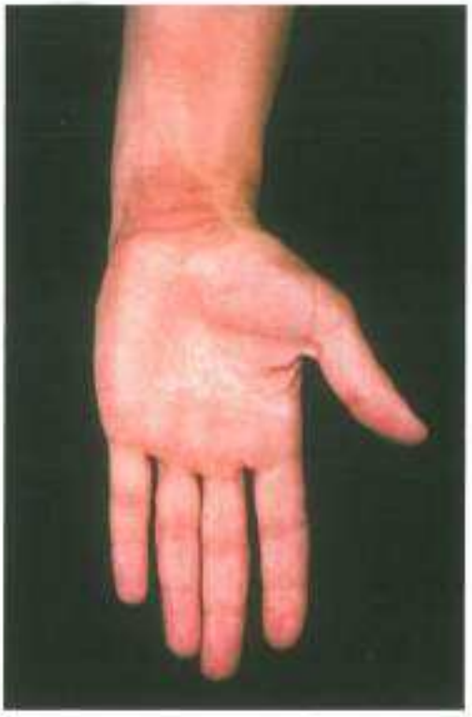


Fig. 27.25 Berloque dermatitis. This is a reaction between bergamot (a psoralen) which is a photosensitizer sometimes found in sunscreens or perfumes and UV light resulting in hyperpigmentation as in this patch on the wrist.

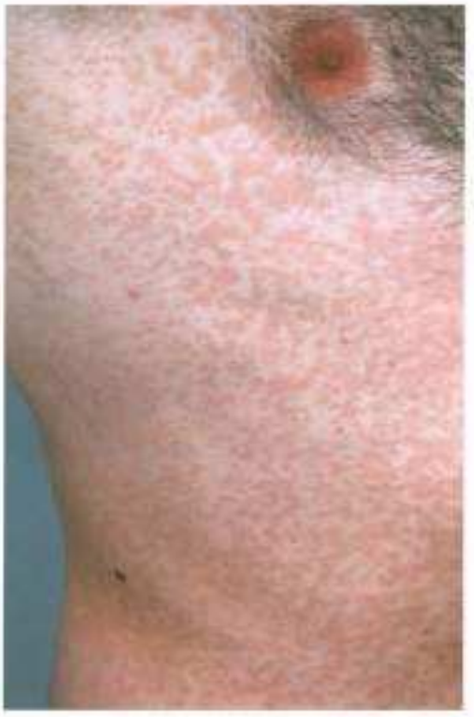


Fig. 27.26 Pityriasis versicolor. Although pigmentation is prominent, scaling was present so this is not postinflammatory where the skin would otherwise be normal. This was pityriasis versicolor.

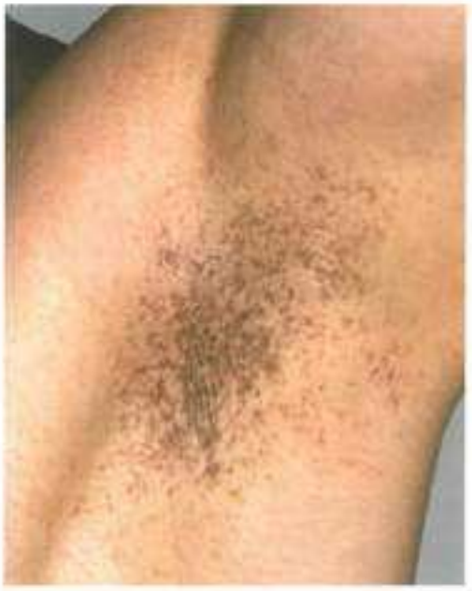


Fig. 27.27 Dowling–Degos disease. A reticulate pigmentation is a striking feature in the flexures. It is probably part of a spectrum of pigmentary anomalies of unknown aetiology.

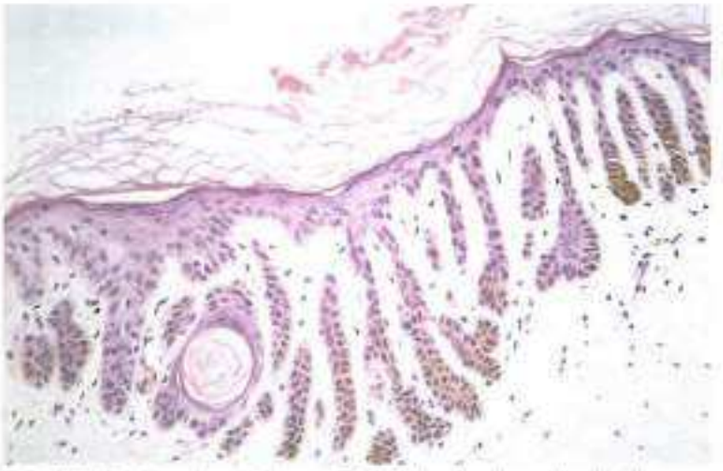


Fig. 27.28 Dowling–Degos disease. The histology has been described by Wilson-Jones as 'demonstrating dusky, dappled disfigurements and disclosing digitate downgrowths delving dermally'.

Known as *Dowling–Degos disease*, it is occasionally generalized with hypopigmented papules. If there is acantholysis histologically, it is known as *Galli–Galli disease*.

Clinical Features

Symptoms

A discoloration in the flexures, neck, axillae, antecubital fossae, submammary regions and groin. There may also be comedone-like dark follicular papules around the neck and margins of the axillae and epidermal or tricholemmal cysts. There may be perioral acneiform pitting, which is most prominent at the angles of the mouth, and occasionally Becker's naevi.

Morphology

There is a reticulate macular hyperpigmentation.

Distribution

Antecubital fossae, axillae, neck (Fig. 27.27), inframammary areas and inner aspects of the thighs are affected.

Management

The histology is helpful. There is a filiform downgrowth and often clubbing of the rete pegs with increased melanin at their tips (Fig. 27.28). There may be dermal melanosis. The condition should be easily distinguished from acanthosis nigricans, where there are velvet-like plaques in the flexures with skin tags.

The differential diagnosis includes two conditions, which may be part of the same spectrum:

- **Reticulated acropigmentation of Kitamura**. It is also inherited as an autosomal dominant and there are similar mutations in KRT5. There are reticulate atrophic brown macules on the backs of the hands and feet

Fig. 27.29 Reticulated acropigmentation of Kitamura. There are reticulate brown macules in acral areas. This is due to mutations in the KRT 5 gene. (Courtesy of Dr Elisabeth Higgins.)

(Fig. 27.29), palmar pits and broken epidermal ridges. There is diffuse basal cell hyperpigmentation (as opposed to being limited to the tips of the rete ridges).

- **Haber's syndrome** Haber's syndrome is characterized by pigmented keratotic papules in the axillae but also on the neck and torso with a persistent red face and pitted scars on the face. There is no specific treatment.

Other conditions which should be considered include:

- **Dyschromatosis symmetrica hereditaria** (syn. *reticulate acropigmentation of Dohi*) It is common in the Japanese and Chinese and is due to a defect in the double-stranded RNA-specific adenosine deaminase (DSRAD) gene on chromosome 1p 11-12. There are a mixture of hyper- and hypopigmented macules of various sizes (on the backs of the hands and dorsa of the feet). Histologically there is diffuse basal cell hyperpigmentation and pigmentary incontinence. There is a generalized form (*dyschromatosis universalis hereditaria*), which may be related but starts earlier but does not involve the extremities. It is also an autosomal dominant but the defect is on 6q 24.2-25.2.

Other causes of reticulate pigmentation are:

- **Dyskeratosis congenita** (Ch. 20)
- **Naegeli–Franschetti–Jadassohn syndrome** A rare autosomal dominant ectodermal dysplasia secondary to a defect in the keratin 14 gene, resulting in increased apoptotic activity in the basal cell layer (KRT5 and 14 maintain the integrity of basal keratinocytes). It results in hypohidrosis (and therefore heat intolerance), dental anomalies (early loss of teeth), finger and toenail dystrophy, absent dermatoglyphics and palmoplantar hyperkeratosis. The pigmentation is extensive on the trunk by the age of two and fades during adolescence. It can be widespread but usually is obvious around the mouth and eyes.

ERYTHEMA DYSCHROMICUM PERSTANS

A disorder characterized by a widespread symmetrical eruption of ash-grey-coloured patches in pigmented races.

Aetiology

The cause is unknown. It occurs in both sexes and may occur at any time. It is not common. Histologically, there is vacuolar degeneration of the basal cells. The pigment is to be found in the epidermis and there is pigmentary incontinence. There is a lymphohistiocytic infiltrate around dermal vessels and many melanophages are present. The disorder is presumably postinflammatory in origin. It is possibly secondary to lichen planus.

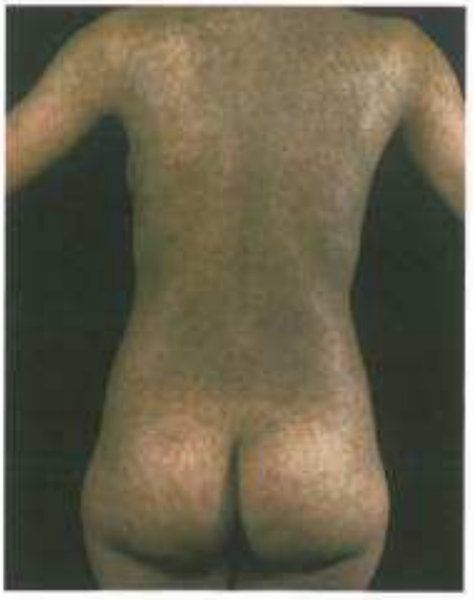


Fig. 27.30 Ashy dermatitis. The patches are ash-grey in colour and may become confluent. The trunk is especially affected. (Courtesy of Prof. E. Wilson Jones, the Institute of Dermatology)

Clinical Features

Symptoms

A pigmentation of the skin.

Morphology

Symmetrical, often figurate, ashen-coloured patches occur, varying from a few millimetres to several centimetres in diameter (Fig. 27.30).

Distribution

Particularly on the trunk.

Management

A skin biopsy is helpful. The diagnosis is usually suspected after known causes of postinflammatory hyperpigmentation have been excluded. There is no treatment and it tends to persist.

POIKILODERMA OF CIVATTE

A mottled pigmentation that occurs on the sides of the neck, particularly in women.

Aetiology

The cause is not clear but it is thought to be caused by photosensitizing chemicals present in perfumes that have been applied previously to the skin. Certainly, sunlight is an important factor. It is relatively common in adult women.

Clinical Features

Symptoms

A pigmentation on the neck.

Morphology

A mottled pigmentation, sometimes with atrophy and telangiectasia.

Distribution

Sides of the neck (Fig. 27.31) and very occasionally on the face.

Management

Perfumes should be avoided and photoprotection is advised. Lasers are beneficial in some cases.

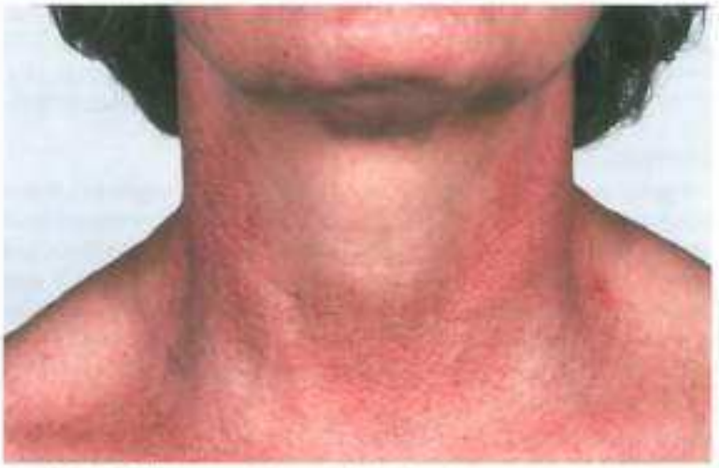


Fig. 27.31 Poikiloderma of Civatte. A reticulate pigmentation, atrophy and telangiectasia occurs most commonly in women on the side of the neck with sparing of the front of the neck.

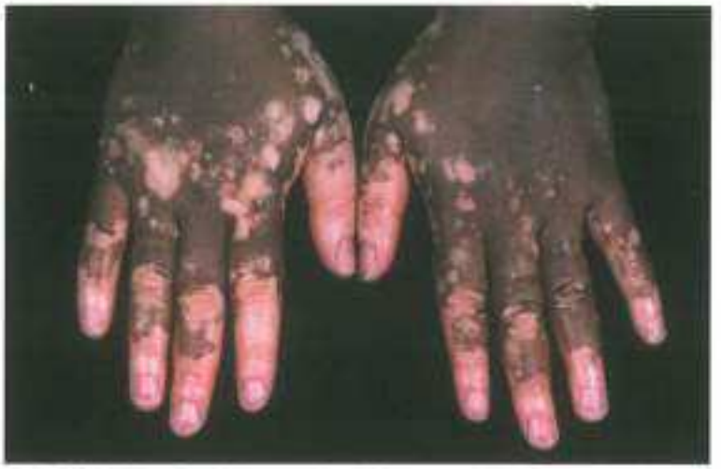


Fig. 27.32 Vitiligo. The lesions are sharply demarcated with irregular borders and have a chalk-white coloration. The lips are often also involved. Treatment is ineffective in this 'lip tip' distribution.

Hypopigmentation

Generalized hypopigmentation occurs in hypopituitarism but is seldom noticed by the patient. The pallor is partly caused by MSH deficiency and partly by the anaemia that accompanies the disease. The deficiency of pituitary trophic hormones results in gonadal failure followed by hypothyroidism and eventually in adrenal insufficiency. Body hair is sparse (males note that they shave less) and the skin is soft, wrinkled and pale. Certain inborn errors of metabolism also result in quite extensive dilutions of skin colour and in particular in albinism and phenylketonuria. Localized loss of pigmentation is a common complaint. Partial loss is known as hypopigmentation and complete loss as depigmentation, of which vitiligo is the best example.

VITILIGO

An acquired destruction of melanocytes that results in white patches on the skin.

Aetiology

The disorder is common (possibly with an incidence of 1%), affects both sexes and, in about a third has a family history. All races are affected. Vitiligo occurs at any age from infancy to old age, but 50% develop it before 20 years of age. It is thought to be an autoimmune disorder as it is associated with thyroiditis, diabetes mellitus, pernicious anaemia, alopecia areata, primary biliary cirrhosis and adrenal insufficiency. Antibodies against melanocyte surface antigens are present and the extent of the disease is proportional to the incidence and level of the antibodies. There are antityrosinase antibodies and increased antibody titres against benzenes, and it is known that structurally related compounds, for example phenols, catechols and hydroquinones, cause depigmentation.

There are also anti-melanin antibodies and an infiltrate of $CD4^+$ lymphocytes in the affected skin in the *Vogt–Koyanagi–Harada syndrome*. This is vitiligo (particularly of the head and neck) occurring in females in the fourth decade, particularly in darkly pigmented races. It has a meningeal phase of aseptic meningitis with an ophthalmic phase that affects visual acuity and a convalescent phase where alopecia, poliosis, vitiligo and cranial nerve dysfunction are associated with dysacusis and tinnitus. This may be followed by chronic recurrent phases of uveitis and other ocular problems. It is rare.

As vitiligo sometimes occurs in a segmental distribution, it is possible that a neurochemical mediator that destroys melanocytes is present. Certainly, there is increased sweating and vasoconstriction in vitiligo, suggesting increased andrenergic activity, and depigmentation occurs in animal models when nerve fibres are collectively severed. Pathologically, there is an absence of melanocytes and melanin in the epidermis. There is failure to stain with DOPA and silver nitrate stains. Cultured melanocytes show various abnormalities and also grow poorly and die prematurely. There is a fourfold increased risk in close biological relatives.

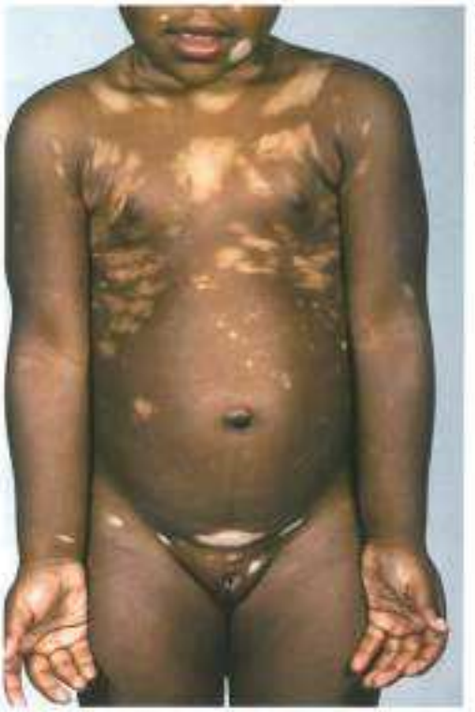


Fig. 27.33 Vitiligo. In the initial stages it may be hypopigmented. The suprapubic patch is completely white however, and this establishes the diagnosis.

Clinical Features

Symptoms

Loss of pigment occurs in the skin with consequent disfiguration.

Morphology

The patches are usually completely depigmented and appear totally white (Fig. 27.32), but not always in the initial stages (Fig. 27.33). There is no other cutaneous change. The lesions are well defined and may have a

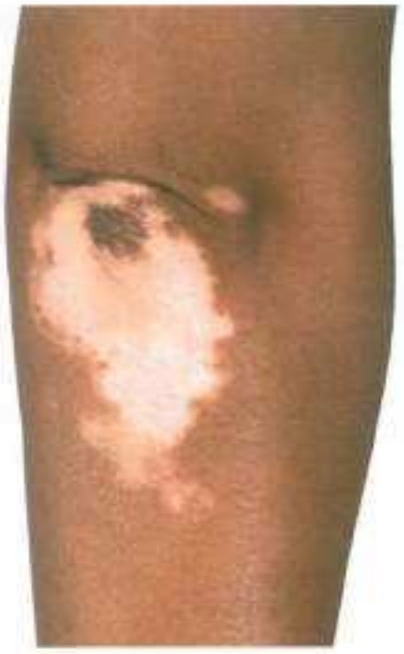


Fig. 27.34 Vitiligo. The lesions may be round or oval and have well-defined margins, often with convex borders.

hyperpigmented margin. They have convex borders, which are oval (Fig. 27.34) or round and of varying sizes. The margins sometimes have an intermediate level of colour, which is known as trichrome vitiligo (Fig. 27.35), or an erythematous ring, which is known as inflammatory vitiligo.

Distribution

Vitiligo is usually symmetrical but occasionally it can be segmental. It may occur anywhere on the body. Frequently it is periorificial in that it occurs around the mouth, lips (Fig. 27.36), nose, eyes, nipples, umbilicus and anus. It may be intertriginous, such as in the groins and axillae. It may occur on extensor surfaces, such as the elbows, knees, fronts of the shins and the backs of the hands and feet; on the flexor surfaces of the wrists and in the oral mucosa as well. Hair growing within vitiliginous patches may appear white.

Almost universal involvement (Figs 27.37 and 27.38) occasionally occurs. Lesions are usually asymptomatic but some patients note a premonitory itch. The patches are liable to sunburn but, surprisingly, not to malignant change. Vitiligo is barely perceptible in the fair-skinned in winter, but tanning of surrounding normal skin heightens the contrast and may reveal it for the first time. The condition may be precipitated by trauma (Koebner phenomenon). Other autoimmune disorders may be present.

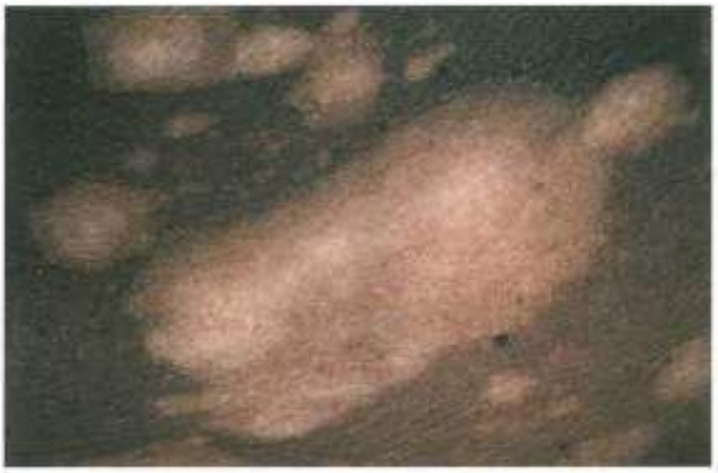


Fig. 27.35 Trichrome vitiligo. This refers to a zone of intermediate colour between the normal and vitiliginous skin. Its significance is obscure.

Fig. 27.36 Vitiligo. Circumorificial vitiligo is common. The lips and oral mucosa may be involved.

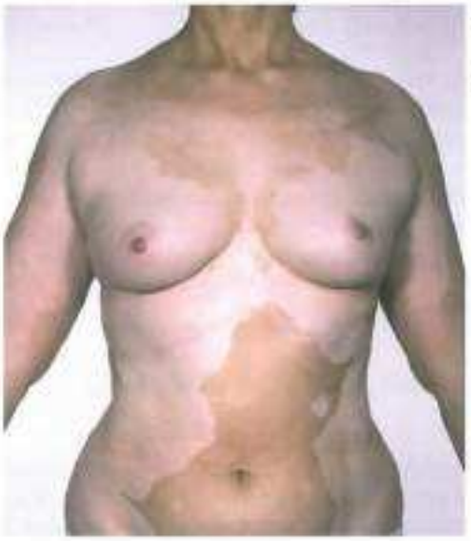


Fig. 27.37 Vitiligo. Vitiligo may be extensive and ultimately become universal.

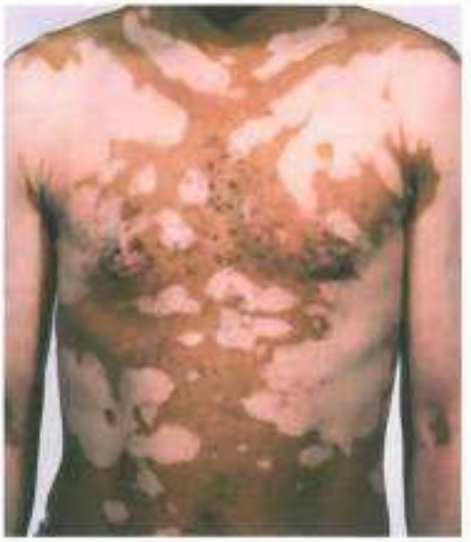


Fig. 27.38 Vitiligo. If PUVA fails, some dark-skinned patients opt for treatment with 20% monobenzylether of hydroquinone in an attempt to whiten the remaining black skin.

Spontaneous repigmentation occurs tantalizingly in a minority, particularly around the hair follicle orifices (Fig. 27.39) but rarely with satisfactory total repigmentation.

Systemic features

Melanocytes are normally present in the eye and depigmented areas are found in the pigmented epithelium and choroid in 40%. There is an increased incidence of uveitis. Melanocytes are also present in the membranous labyrinth at the inner ear and auditory problems, particularly hypoacusis, do occur.

Management

A pseudovitiligo-like depigmentation may occur in patients taking tyrosine kinase inhibitors (e.g. imatinib for Philadelphia +ve chronic myeloid leukaemia) particularly around the eyes (panda eyes Fig. 27.40), but the diagnosis of vitiligo is usually not difficult. In fair-skinned patients, examination under a Wood's light may be necessary to see the extent of the vitiligo. The disorder may be devastating in dark skins, because it is so noticeable that the patient may feel socially ostracized. It is extremely difficult to treat. The prognosis is poor in widespread vitiligo and when the mucosae, fingers and toes (lip tip syndrome) are affected. There is a fair amount of recovery however when the face or neck are involved, particularly in black races. The prognosis in Caucasians, however, is universally poor.

Management consists of:

- **Photoprotection** High-protection factor sunscreens which block ultraviolet A and B are mandatory to prevent contrasting tanning of the surrounding normal skin and burning of the affected skin. They should be applied every day and sun exposure strictly avoided.
- **Topical glucocorticosteroids** Very potent topical steroids are indicated for those areas that potentially may recover, such as the face (Figs 27.41 and 27.42). However, adequate supervision is indicated and the risk of facial steroid side-effects should be explained (although these are unusual if the ointment is applied accurately to the areas of vitiligo).
- **Camouflage** Camouflage with sunscreen that contains make-up (Cover-mark, Keromask) is helpful, especially if the guidance of a camouflage instructor is available. Dihydroxyacetone may be used to stain the vitiligo a more acceptable colour.
- **Psoralens** Photochemotherapy (PUVA) using psoralens topically or systemically has been tried, although phototoxicity (burning and

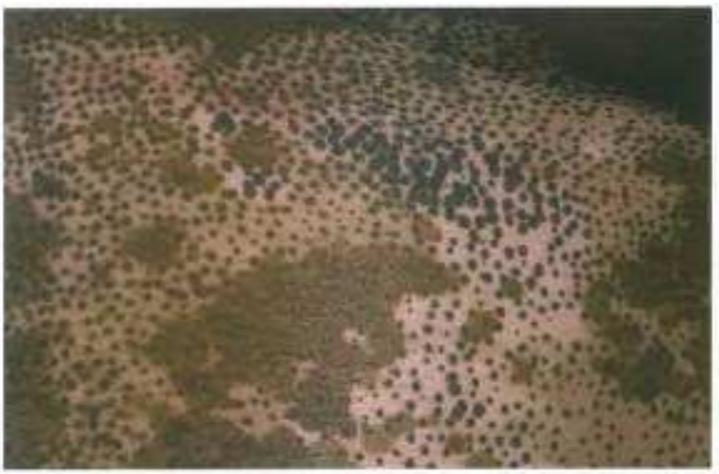


Fig. 27.39 Vitiligo. Repigmentation does occur particularly around hair follicles. Melanocytes in the outer root sheath are immunologically privileged and may not be destroyed by cytotoxic T lymphocytes.

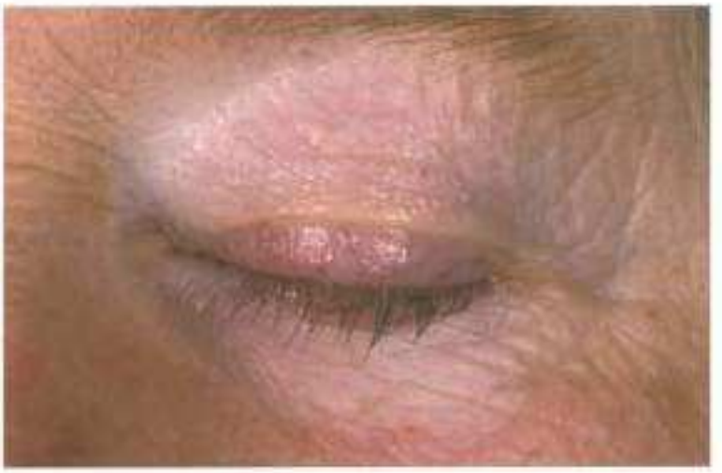


Fig. 27.40 Panda eyes. Tyrosine kinase inhibitors such as imatinib, which have transformed treatment of Philadelphia +ve chronic myeloid leukaemia and other disorders may cause a vitiligo-like depigmentation around the eyes.

Figs 27.41 and 27.42 Vitiligo. Good results may be achieved with superpotent steroids applied accurately daily. The repigmentation shown in Figure 27.42 took 7 months to achieve.

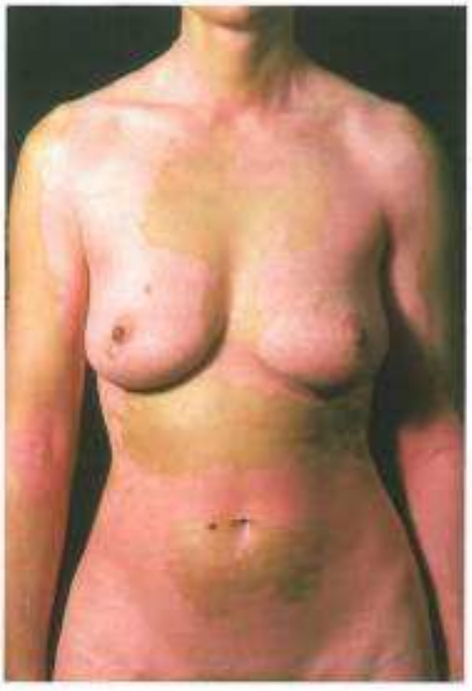


Fig. 27.43 Vitiligo. Because of the lack of melanocytes, individuals will burn readily in the sun. This patient was undergoing treatment with psoralens and ultraviolet light. (Courtesy of St Mary's Hospital.)

blistering) may occur (Fig. 27.43). Treatment is protracted and requires anywhere between 100 and 300 treatments. Those in whom the disease affects the face and neck have a 50% chance (Figs 27.44 and 27.45) of repigmenting (increasing to 80% with over 200 treatments), although for general vitiligo (excluding mucosal or fingers) there is only a 28% chance (increasing to 80% with over 200 treatments). These figures come from North America and not all centres have been so fortunate. In the Middle East and India, patients are instructed to take 8-methoxypsoralen or trimethylpsoralen 2 hours before exposure to the midday sun. The patient exposes the affected skin for increasing periods each day. Treatment has to be continued for months and often years.

- **Narrowband ultraviolet light** Some patients do not tolerate PUVA well. Types IV–VI skins have the best prognosis, especially on the face.
- **Monobenzylether of hydroquinone** This treatment is rarely used. It causes permanent loss of pigment and should be used only for depigmenting residual normal skin in patients with near universal vitiligo (Figs 27.46 and 27.47). It is hazardous because contact and irritant dermatitis may occur in addition to unwanted pigmentary effects.
- **Surgery** Various forms of autologous skin grafting have been used including epidermal from suction blisters. Also melanocytes have been cultured in vitro and then placed on recipient denuded skin.

ALBINISM

An autosomal recessive disorder of tyrosinase metabolism that results in partial or complete failure of melanin production from the melanocytes in the skin and the eyes.

Aetiology

There are nine variants inherited as autosomal recessives and one as a dominant. Essentially, these are based on whether tyrosinase is absent or non-functioning. Melanocytes are present in the skin but fail to produce melanin adequately. Tyrosinase-negative albinism (type 1A) is so-called because plucked hair bulbs incubated with tyrosine do not darken. The hair and skin are white. There is extreme photosensitivity and risk of skin cancer. The eyes are blue-grey at birth and impaired vision is common. In OCA1B tyrosinase is reduced but not absent and although there is little or no pigment at birth (thus resembling OCA1A) subsequently some develops in the skin (but not in warmer areas such as axillae and groin because tyrosinase is temperature sensitive and loses its activity over 35°C). The hair is yellow-red (since it requires less tyrosinase to make enmelanin). There are at least eight other mutations in the tyrosinase gene.

In tyrosinase-positive albinism (type 2), which is the commonest especially in Africa, they do darken and clinically some pigment is formed, particularly in the iris, skin (especially large pigmented lentigines in sun-exposed areas) and hair with increasing age. There are two associated conditions. The *Prader–Willi syndrome* is comprised of hyperphagia, obesity, hypogonadism and mental retardation. The *Angelman syndrome* is OCA2 with microcephaly, ataxia and mental retardation. The skin is not involved in ocular albinism, but deafness is common.

In OCA type 3 there are mutations in the tyrosinase related protein 1 (TYRP1) gene on 9p 23. The patients have a rufous colour with red-bronze skin, ginger-red hair and blue/brown irises. OCA1 and 3 are endoplasmic reticulum (ER) retention diseases where the abnormal proteins (tyrosinase or TYRP1) never leave the ER to become incorporated into the melanosomes.

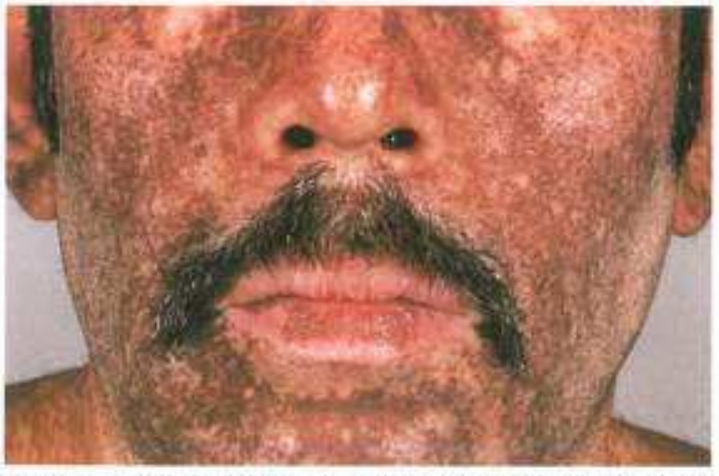


Fig. 27.44 Vitiligo. Prolonged photochemotherapy (both systemic psoralens and topical psoralens plus ultraviolet light) is sometimes helpful in dark skins.

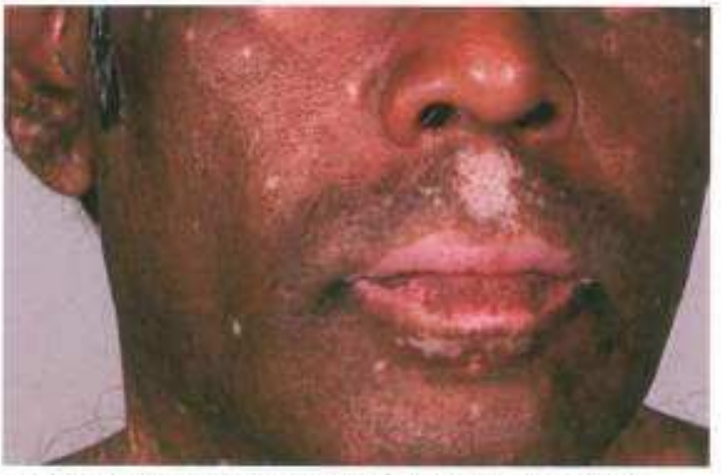


Fig. 27.45 Vitiligo treated with systemic PUVA. PUVA may be effective (Fig. 27.44) but many treatment exposures are required. Narrowband ultraviolet B has also been reported as being effective.

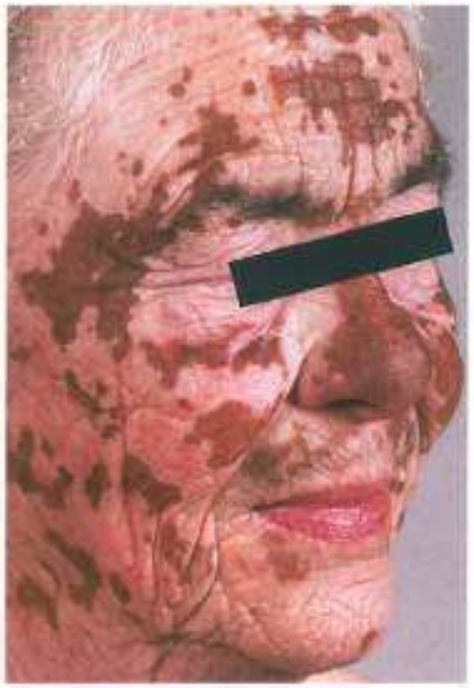


Fig. 27.46 Extensive vitiligo. This South African lady had disfiguring vitiligo and requested that her normal dark skin colour should be depigmented.

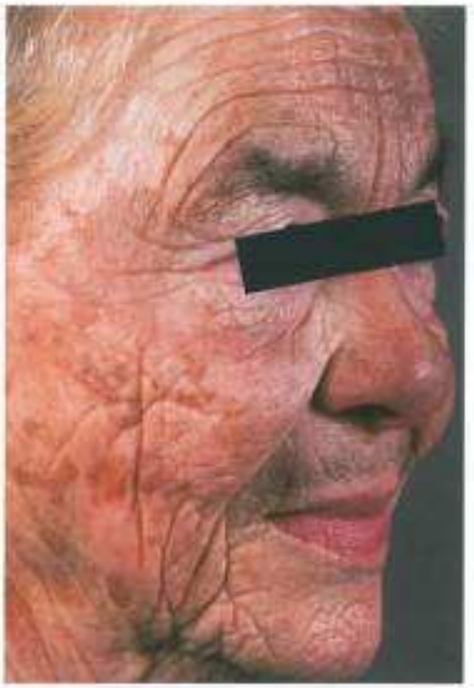


Fig. 27.47 Extensive vitiligo. She (Fig. 27.46) derived some benefit from monobenzylether of hydroquinone used to depigment permanently the remaining normal pigmented skin on her face.

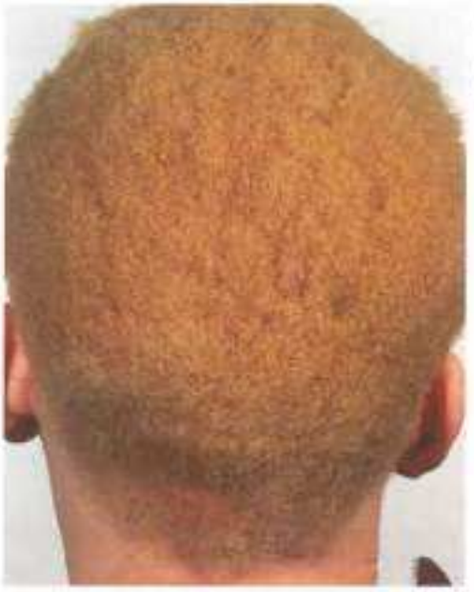


Fig. 27.48 Albinism. The skin is almost white and the hair is flaxen yellow because of non-functioning tyrosinase.

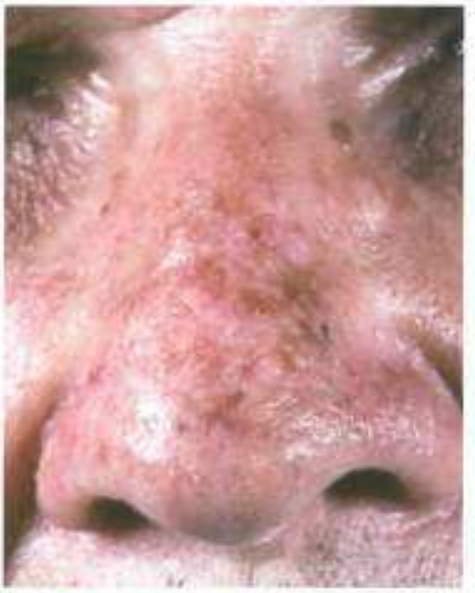


Fig. 27.49 Albinism. The lack of photoprotective melanocytes leads to skin cancer early in life, especially squamous cell carcinoma.

OCA type 4 is most common in Japan. Phenotypically the patients resemble OCA2. There is a defect in the membrane-associated transporter protein (MATP).

The *Chediak–Higashi syndrome* is a rare autosomal recessive disorder of infancy and childhood resulting in immunodeficiency (with recurrent pyogenic infections), mild bleeding diathesis and subsequent lymphoproliferation with pancytopenia and haemophagocytic syndrome, which is fatal without bone marrow transplantation. There is also progressive neurological damage. The skin colour is diluted but with hyperpigmentation in sun-exposed areas, silvery hair, photophobia and nystagmus. There are mutations in the lysosomal trafficking regulator (LYST) gene, which results in giant intra-cytoplasmic granules in the melanosomes, platelet dense granules and leucocyte cytolytic granules.

The *Hermansky–Pudlak syndrome* occurs primarily in Puerto Ricans and is a platelet storage deficiency manifesting as easy bruising and a bleeding tendency associated with oculocutaneous albinism, eventuating in fatal pulmonary fibrosis.

Clinical Features

Symptoms

A marked loss of pigmentation of the skin, hair and eyes.

Morphology

In tyrosinase-negative type IA, the skin is pink and the hair is white. In tyrosinase-positive type 2, some pigment is present and the hair is flaxen yellow (Fig. 27.48). Dark brown freckles (Fig. 27.49) develop with age in

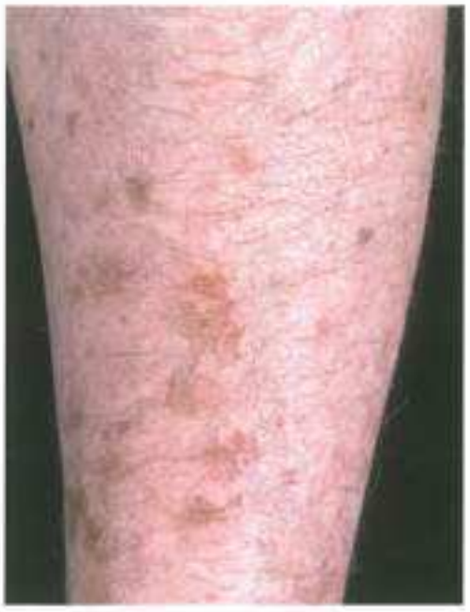


Fig. 27.50 Albinism. Dark brown patches of pigmentation do occur in sun-exposed skin in tyrosinase-positive oculocutaneous albinism.

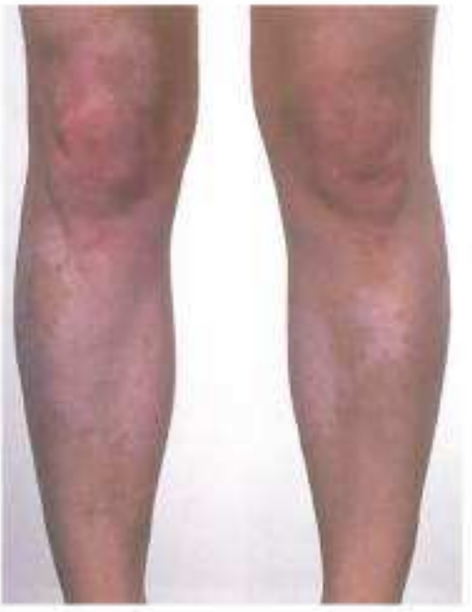


Fig. 27.51 Piebaldism. Hypermelanotic macules occur within hypomelanotic patches on the upper regions of the shins.

sun-exposed areas (Fig. 27.50). In the yellow mutant type (OCA1B), the hair is yellow-red by 1 year of age.

Systemic features

Photophobia, squinting and nystagmus are present.

Skin cancers, particularly actinic keratoses and squamous cell carcinomas but occasionally melanoma, are problematic in tropical countries and early demise may occur from these tumours.

Management

There is no specific therapy. However, photoprotection, regular surveillance of the skin for malignant change and ophthalmic care are essential.

PIEBALDISM

An autosomal dominant disorder of melanoblast migration or differentiation that results in vitiligo-like patches of the skin and hair.

Aetiology

The disorder is inherited as an autosomal dominant. It is secondary to the lack of migration or survival of melanocytes in the inner ear, iris and midportion of the forehead and extremities. It depends on interactions between the mast cell growth factor (stem cell growth factor of Steel) and the KIT receptor on melanocytes. There is a mutation in the KIT proto-oncogene (localized on chromosome 4q 11-12), which encodes a tyrosinase kinase family of transmembrane receptors on the surface of melanocytes, which need to be activated by the Steel factor for their normal development.

Waardenburg's syndrome is an autosomal dominant condition with skin lesions very similar to piebaldism, including a white forelock, lateral displacement of the medial canthi, hyperplastic medial eyebrows, a hypertrophied nasal root, and light blue iris associated with congenital receptive deafness. Patients may also have Hirschsprung disease (congenital megacolon) due to lack of migration or survival of enteric ganglion cells which are also derived from the neural crest.

Clinical Features

Symptoms

White patches present at birth.

Morphology

Hypermelanotic macules occur within vitiligo-like hypomelanotic macules.

Distribution

This is quite characteristic and involves the middle of the upper arms down to the wrists, mid-thighs to the mid-calves or shins (Fig. 27.51) and the centre of the back. There is usually a white forelock of hair, which is known as poliosis.

Management

There is no treatment.

Postinflammatory hypopigmentation

The common causes of temporary failure of pigmentation following inflammation are eczema (Fig. 27.52), pityriasis alba (see below), pityriasis versicolor (Fig. 15.17), sarcoidosis (Fig. 22.11), mycosis fungoides (Fig. 27.53) and leprosy.

PITYRIASIS ALBA

A common condition of patches of hypopigmentation limited to the face that occur in childhood or adolescence, particularly in darker skin.

Aetiology

It is possibly caused by a preceding eczema; however, this is rarely visible and the children are not atopic, and it does not respond to topical steroids.

Clinical Features

Symptoms

Loss of pigment on the face in a young person.

Morphology

Patchy hypopigmentation without any surface changes of inflammation or scaling.

Distribution

The face, especially the cheeks (Figs 27.54 and 27.55).

Management

There is no effective treatment but ultimately it clears spontaneously after a number of years.

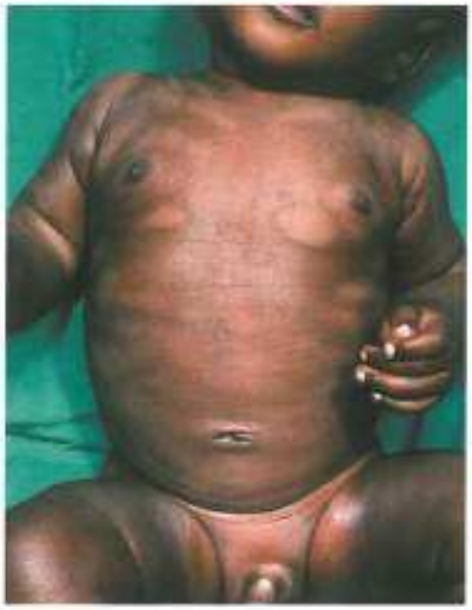


Fig. 27.52 Postinflammatory hypopigmentation secondary to seborrhoeic eczema. Temporary loss of pigment occurs particularly following eczema in dark skins.

Fig. 27.53 Mycosis fungoides. Hypopigmented macules and patches of various shapes and sizes are present. Close inspection of the lesions may reveal atrophy and scaling. Biopsy is mandatory in unexplained pigmentary disorders. This is mycosis fungoides.

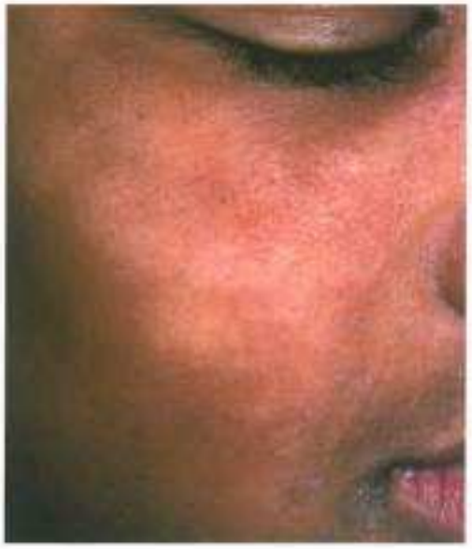


Fig. 27.54 Pityriasis alba. There are asymmetrical patches of partial loss of pigment without any surface or obvious inflammatory changes. It is most common in black skins.

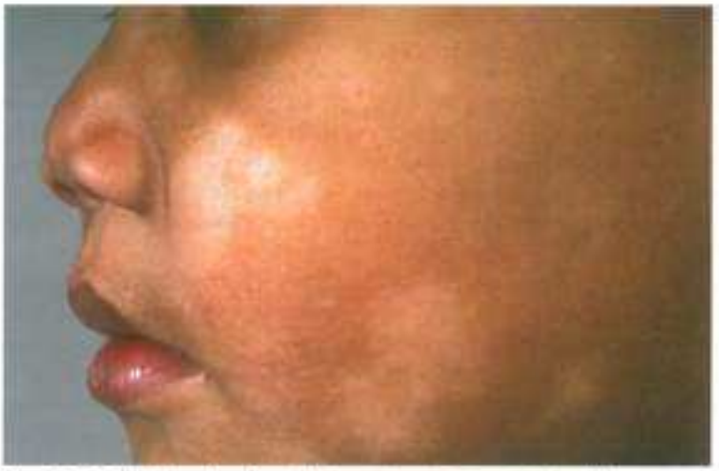


Fig. 27.55 Pityriasis alba. A patchy hypopigmentation on the cheeks is common in children and adolescents. Although thought to be secondary to eczema, this is rarely observed. It eventually recovers.

IDIOPATHIC GUTTATE HYPOMELANOSIS

A common disorder of focal loss of pigment on the limbs, probably caused by excess solar exposure.

Aetiology

The disorder is common in sun-damaged Caucasians, particularly on the lower legs but also arms. It is striking in dark skins, probably as an effect of ultraviolet light for it is rarely seen in West Indians raised in England but is common in those who spent their childhood in the Caribbean.

Clinical Features

Symptoms

White spots particularly on the legs.

Morphology

Well-circumscribed small white macules (Fig. 27.56).

Distribution

The shins, arms and occasionally the abdomen.

Management

The lesions are quite harmless but there is no treatment.

Fig. 27.56 Idiopathic guttate hypomelanosis. Well-circumscribed, white macules occur particularly on the lower legs. It is probably secondary to excess exposure to ultraviolet light.

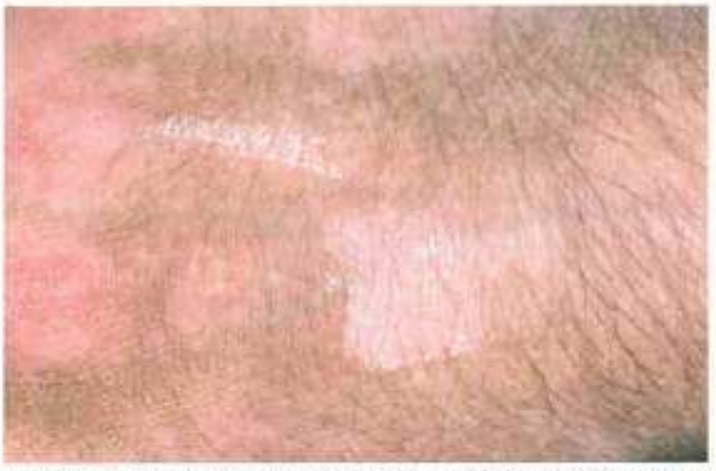


Fig. 27.57 Exogenous pigment. This adolescent complained of pigmentation on the hand. The dirt was easily scraped away to reveal normal skin underneath.

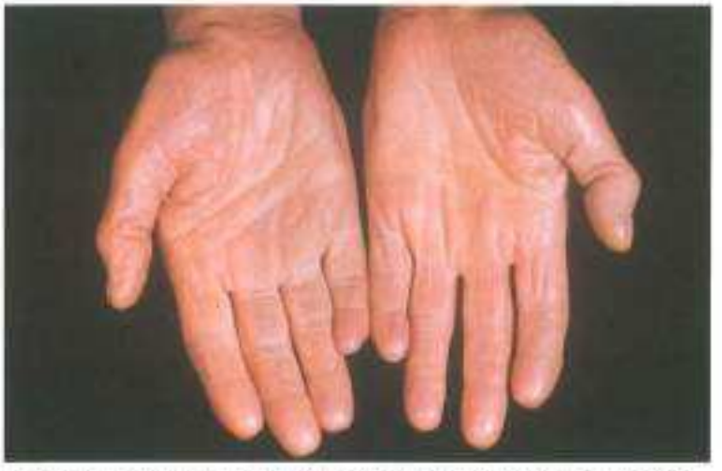


Fig. 27.58 Carotoderma. A yellow discoloration of the skin occurs. The palms are particularly affected. (Courtesy of the Institute of Dermatology.)

Non-melanin pigmentary disorders

Jaundice is the most common non-melanin pigmentation of the skin. The yellow discoloration results from the deposition of bile pigments in the skin and sclerae. Carotenaemia also causes yellow discoloration. The pigmentation of haemochromatosis is partly from melanin but also from iron deposition in the skin. Localized deposition of iron is common as a result of stasis eczema and ulceration of the lower legs and is caused by haemosiderin deposition following extravasation of red blood cells. Haemosiderin is also deposited in the skin of the lower limbs secondary to capillaritis.

Mepacrine, an antimalarial drug, causes yellow discoloration of the skin. Silver may be ingested by those working with the metal and, deposited in the skin, produces a slate-blue discoloration; this is particularly accentuated in sun-exposed areas. Gold very rarely produces a blue-grey discoloration when given parenterally. Exogenous pigments may become embedded in the skin during tattooing or from coal dust in miners, and occasionally patients are concerned about a pigmentation that is simply ingrained dirt (Fig. 27.57). Various chemicals stain the skin temporarily, e.g. iodine, dihydroxyacetone, dithranol and potassium permanganate.

CAROTENAEMIA

A yellow discoloration secondary to an excess of the naturally occurring pigment carotene.

Aetiology

This is most commonly seen in food faddists, including anorexics, who eat a large number of carrots or oranges. A similar orange-yellow discoloration (carotenoderma) may result from excess tomato or papaya ingestion. The carotene, which is a naturally occurring pigment of the skin, discolours keratin an orange colour. It is particularly obvious on the palms and soles. Beta-carotene (given orally in the treatment of erythropoietic protoporphyria) and yellow tablets (including zantac) produce a similar discoloration. A yellow discoloration also occurs in hypothyroidism, nephritis and diabetes mellitus. It is caused by an inability to convert β carotene into vitamin A.

Clinical Features

Symptoms

A yellowing of the palms and soles (Fig. 27.58).

Morphology

A diffuse yellow pigmentation.

Distribution

This is most noticeable on the palms and soles.

Management

Patients should be advised to reduce their intake, in order to minimize the risk of hypervitaminosis A.

Skin disorders associated with pregnancy and the reproductive system

28

Pregnancy

There are a number of cutaneous associations with pregnancy:

- **Spider naevi and palmar erythema** (Fig. 28.1) These usually disappear after delivery.
- **Generalized pigmentation** This occurs and is particularly heightened in already pigmented areas, such as the areola (Fig. 28.2), genitalia and linea nigra (Fig. 28.3).
- **Localized pigmentation** This may occur on the face (*chloasma*) (Fig. 28.4).
- **Benign pigmented naevi** During pregnancy, these may increase in number and in size and skin tags frequently develop.
- **Striae** Abdominal striae are common.
- **Hair** Growth of hair is more luxuriant since more hairs are in anagen than normal. There is frequently a compensatory precipitation of hairs into telogen after delivery, so that many women notice hair loss (*telogen effluvium*) around 3 months postpartum.
- **Skin disorders** Many skin disorders, for example acne, eczema and psoriasis, are improved by pregnancy but not always.
- **Candida vulvovaginitis** is common.
- **Genital warts** These tend to grow during pregnancy, probably as a result of anogenital hyperaemia and the immunosuppression of pregnancy necessary to prevent fetal rejection.
- **Folliculitis** A pruritic sterile folliculitis is common in primigravida. It often settles before delivery but may respond to topical steroids or ultraviolet B. It is associated with a twofold increase in a male outcome.

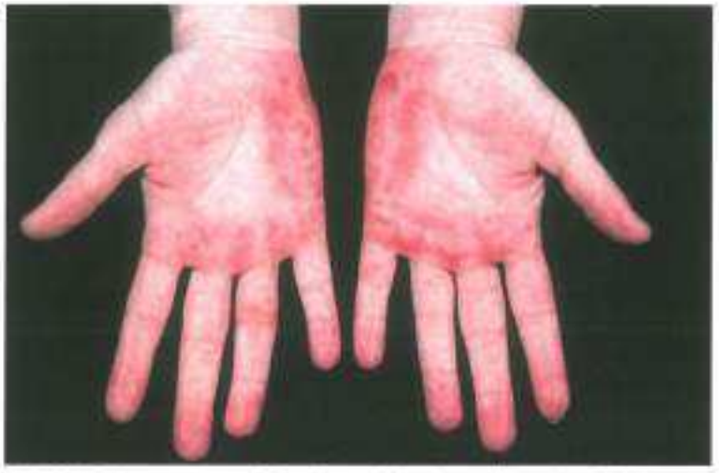


Fig. 28.1 Palmar erythema. There is marked redness of the palms. This is common in pregnancy and quite harmless. It is part of the hyperdynamic circulation and disappears with parturition.

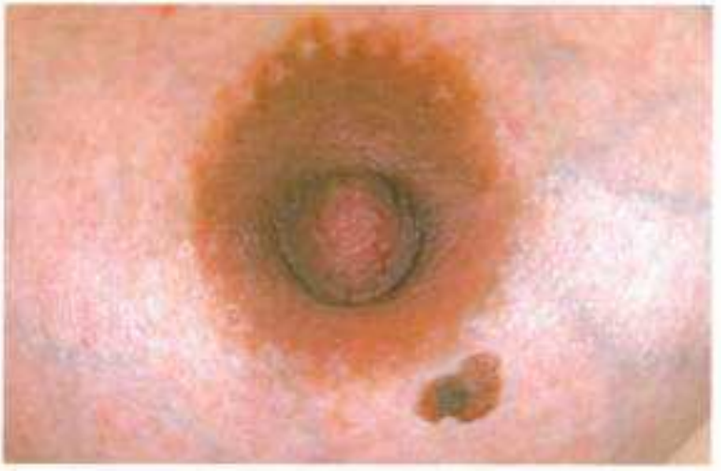


Fig. 28.2 Pigmentation. The areolae darken during pregnancy. The lesion on the breast is a seborrhoeic wart.

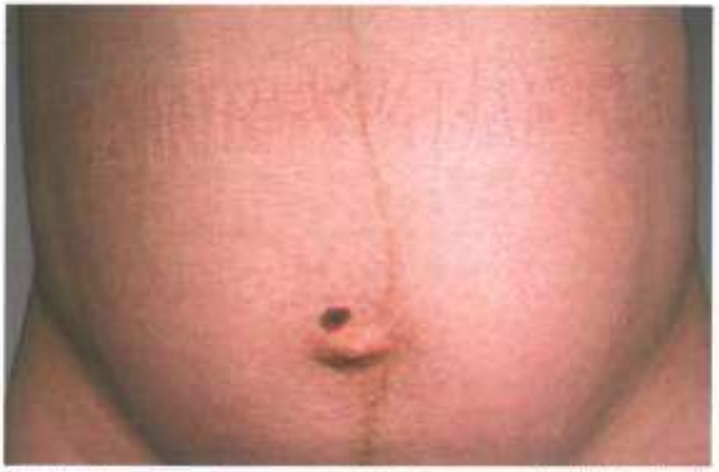


Fig. 28.3 Linea nigra. In pregnancy the skin darkens generally and in a localized manner on the areola, genitalia and in a line above and below the umbilicus (linea nigra). Moles darken too.

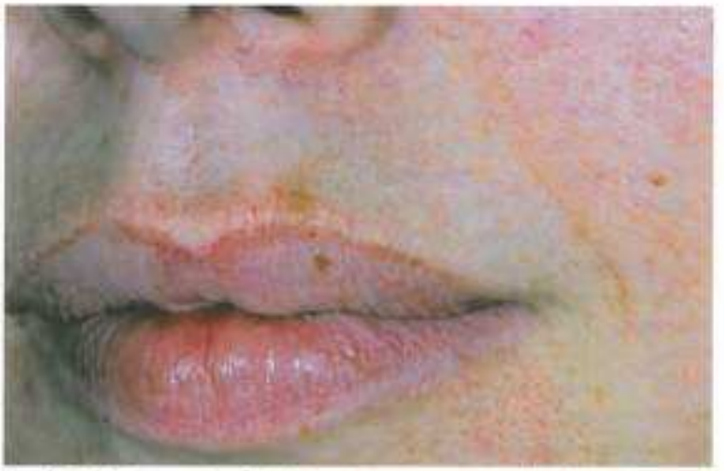


Fig. 28.4 Chloasma. Localized pigmentation may occur on the forehead, nose, cheeks and lips, here simulating a moustache.

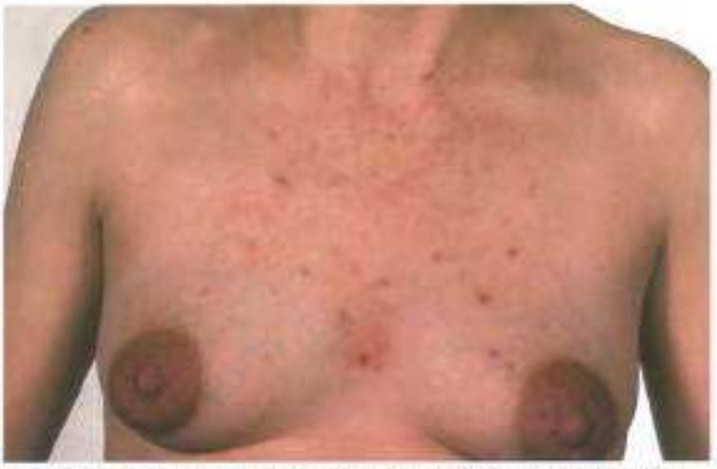


Fig. 28.5 Prurigo gravidarum. Scratch marks are visible. It occurs in the last trimester and is recurrent. Liver function tests are normal.

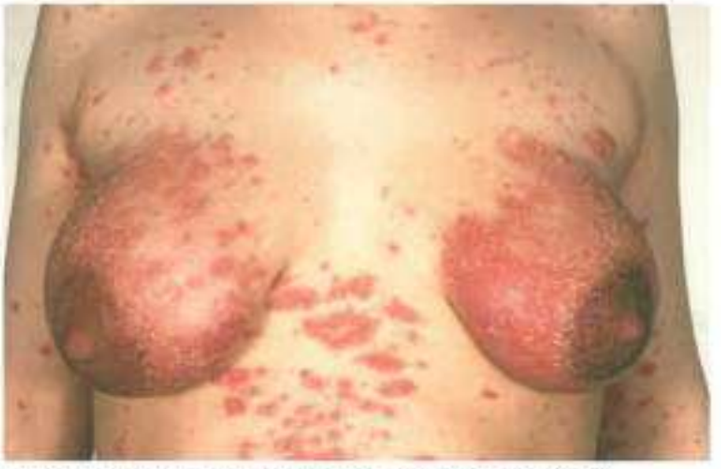


Fig. 28.6 Generalized pustular psoriasis. The eruption tends to be symmetrical. There is a considerable risk to the fetus (stillbirth, neonatal death or abnormalities). Treatment is unsatisfactory.

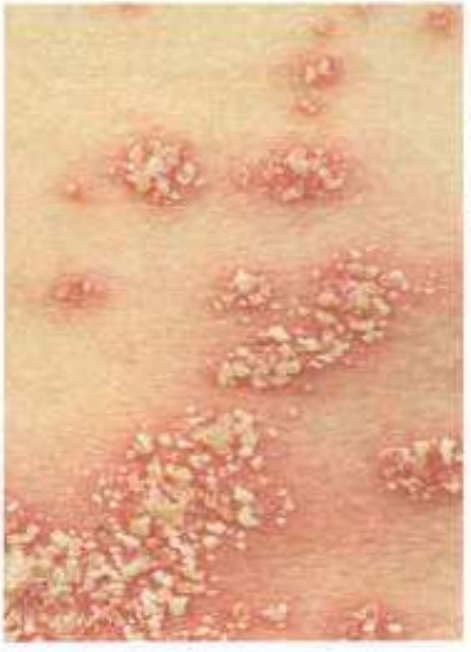


Fig. 28.7 Generalized pustular psoriasis. Formerly known as impetigo herpetiformis, this is identical clinically to pustular psoriasis. There are a myriad of pustules arising on acutely inflamed skin.

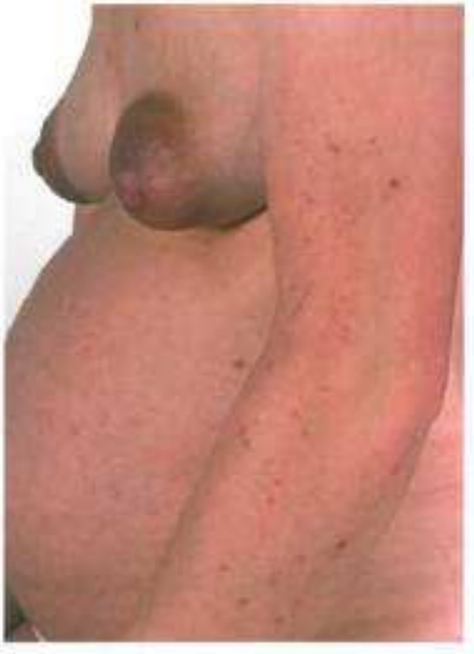


Fig. 28.8 Obstetric cholestasis. The skin is itchy generally, particularly at night and including the palms and soles. Excoriations (scratch marks) are prominent.

- **Papular dermatitis of pregnancy of Spangler** This was reported with a 30% fetal mortality, elevated serum and urinary human beta chorionic gonadotrophin levels, reduced serum oestradiol and reduced serum hydrocortisone. It has largely been discounted.
- **Maternal infections** Certain maternal infections known by the acronym TORCH (toxoplasma, rubella, cytomegalovirus and herpes simplex virus) have important implications for the fetus. Other infections of significance for mother and child include syphilis and Lyme disease (at any time during pregnancy), group B streptococci and *Neisseria gonorrhoeae* at delivery, and varicella zoster, parvovirus and human papillomaviruses.
- **Itching** This is common, particularly over the lower abdomen. The term *prurigo gravidarum* (Fig. 28.5) is best retained for itching without liver abnormalities.
- **Generalized pustular psoriasis** (Figs 28.6 and 28.7) Previously known as *impetigo herpetiformis*, this is a rare but serious generalized pustular disorder of pregnancy with a significant fetal and maternal mortality. It differs slightly clinically from other forms in that there are symmetrical grouped minute pustules on an acutely inflamed skin, starting particularly in the flexures, especially the inguinogenital. The lesions extend centrifugally, drying centrally, and may form plaques which erode and become crusted and vegetating. There may be a severe constitutional disturbance, with fever and occasionally cardiac and renal failure. There is hypocalcaemia and reduced serum vitamin D, probably as a result of malabsorption. The risks of placental insufficiency are high, leading to stillbirth or neonatal death or fetal abnormalities. Management is complicated partly because the disorder seems to be unresponsive to the agents that are effective in other forms, but partly because of concerns for the fetus. The retinoids are teratogens and methotrexate also carries some risk. Systemic PUVA is best avoided, but topical PUVA and narrowband ultraviolet light can be tried. Systemic steroids are considered to be least hazardous for the fetus, but may not work. Ciclosporin may be effective.
- **Obstetric cholestasis** The itching, which is worse at night, occurs in the last trimester, particularly the last month, and affects the palms and soles as well as the extensor surfaces of the limbs (Fig. 28.8) and sometimes the trunk. There are widespread excoriations with small closely grouped papules. The mother is healthy apart from deranged liver function tests and elevated total serum bile acids. There are fetal complica-

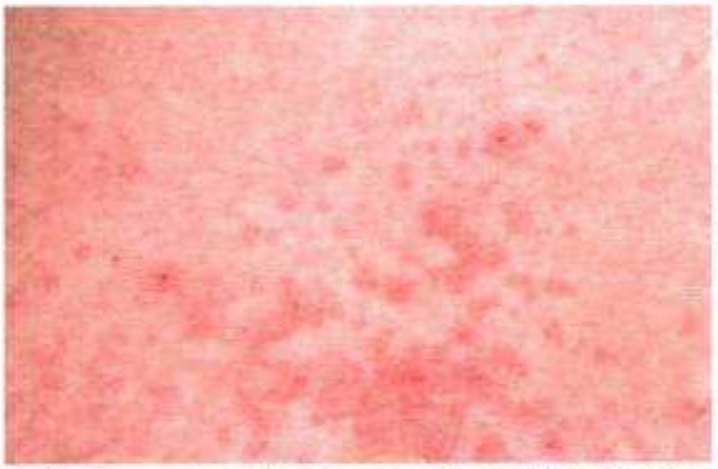


Fig. 28.9 Polymorphic eruption of pregnancy. There are very itchy, urticarial papules and plaques particularly on the limbs. It begins in the last trimester, occurs only in the first pregnancy and is relieved by parturition.

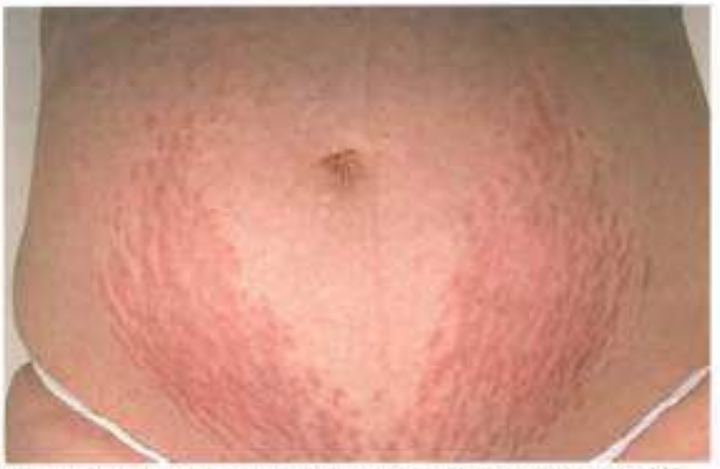


Fig. 28.10 Polymorphic eruption of pregnancy. Formerly known as pruritic urticarial papules and plaques of pregnancy, it begins in the abdominal striae which are very red. Note the periumbilical sparing.

tions (prematurity, fetal distress and stillbirth) secondary to anoxia caused by decreased elimination of toxic bile acids and maternal postpartum haemorrhage. Induction at 38 weeks of gestation can dramatically alter fetal prognosis. The itch disappears within 24 hours of delivery. It is a genetically linked hormonally induced reversible cholestasis. Ursodeoxycholic acid reduces the pruritus and mortality.

- **Prurigo of pregnancy of Besnier** This is probably a manifestation of atopy. There are excoriated nodules on the trunk and limbs, which usually disappears with delivery. It can occur in any pregnancy and in either the second or third trimester.
- **Polymorphic eruption of pregnancy** This condition is common and is described in detail below.
- **Pemphigoid gestationis** This is rare but is also described below.

The important distinguishing features of pregnancy eruptions are:

- **Time of onset** The majority can start at any time, but prurigo gravidarum is more common in, and polymorphic eruption (PUPPP) is confined to, the last trimester.
- **Recurrences** All may recur except PUPPP, which only occurs in the first pregnancy.
- **Fetal outcome** It is excellent in prurigo gravidarum and PUPPP (although twins are more common). It is poor in pustular psoriasis. Stillbirth and haemorrhage are associated with obstetric cholestatis after 38 weeks and stillbirth occasionally occurs in pemphigoid gestationis.

Polymorphic eruption of pregnancy

A common, essentially urticarial eruption that commences in the abdominal striae late in the first pregnancy.

Aetiology

It is possibly caused by microchimerism since fetal cells pass to the mother during pregnancy and persist for decades. Maternal cells also are transmitted to the fetus and persist until adult life. It is associated with excess weight gain during pregnancy. It affects young primigravidae and commences in the last trimester between 35 and 39 weeks. It does not recur and is hazardous to neither fetus nor mother. Direct immunofluorescence is negative. There is a 14% risk of multiple fetuses. It is also known as *pruritic urticarial papules and plaques of pregnancy* (PUPPP).

Clinical Features

Symptoms

It is extremely itchy and begins in the abdominal striae.

Morphology

There are erythematous papules, plaques and urticarial wheals (Fig. 28.9).

Distribution

The lesions occur on the limbs and under the breasts. The abdominal striae are very red, but the periumbilical region is spared (Fig. 28.10).

Management

It disappears with delivery or shortly thereafter. Antihistamines, topical steroids, and 2% menthol in aqueous cream may be helpful. Systemic steroids are sometimes required. Early induction gives rapid relief.

Pemphigoid gestationis

A rare autoimmune subepidermal blistering disorder associated primarily with pregnancy.

Aetiology

The estimated incidence of pemphigoid gestationis is approximately 1 in 100 000 pregnancies. It usually commences in the second trimester but may start as early as the second month or as late as a week postpartum. It recurs in subsequent pregnancies. It may be exacerbated postpartum by oral contraceptives or menstruation. It has been described in association with choriocarcinoma or hydatidiform mole. Linear deposits of C3 are found at the lamina lucida in all those affected and circulating IgG antibodies in 40%. The target antigen is the 180 kDa bullous pemphigoid antigen 2. A circulating IgG antibody (the herpes gestationis factor), has been found in the majority of patients using indirect immunofluorescence. This antibody avidly fixes complement. Clinically, the eruption is identical to that of bullous pemphigoid and, consequently, is now known less often as *herpes gestationis*. However, there are enough differences from bullous pemphigoid to suggest that pemphigoid gestationis is a separate entity. Its occurence in youth and in pregnant women and its association with oral contraceptives is a very different clinical picture from that of bullous pemphigoid of the elderly. Also, isolated necrotic, basal keratinocytes are found in pemphigoid gestationis but not in bullous pemphigoid. The herpes gestationis factor also differs from those antibodies found in bullous pemphigoid. There is an increased association with HLA-A1, HLA-B8 and HLA-DR3 phenotypes, which is not found in bullous pemphigoid. Pemphigoid gestationis is associated with other autoimmune diseases, such as autoimmune thyroiditis and pernicious anaemia.

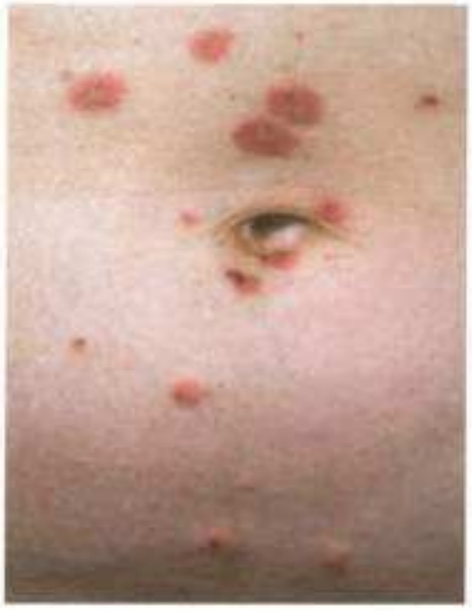


Fig. 28.11 Pemphigoid gestationis. The condition usually starts on the abdomen and involves the umbilicus unlike PUPPP where there is periumbilical sparing.

Clinical Features

Symptoms

There are very itchy blisters, classically beginning around the umbilicus.

Morphology

Urticarial papules and polycyclic wheals (Fig. 28.11) ultimately become tense vesicles (Fig 28.12) or bullae (Fig. 28.13).

Distribution

The lesions occur symmetrically over the abdomen, back, buttocks, arms and legs (Fig. 28.14), becoming widespread.

Management

Immunofluorescence for the specific antigens is invaluable for diagnosis (Fig. 28.15). Oral glucocorticosteroids are usually necessary, starting at 40 mg prednisolone and tapering to 12.5–15 mg daily until the postpartum period. It is sometimes necessary to increase the steroids at the time of delivery because of a postpartum flare. Although an increased incidence of prematurity and fetal mortality has been described, there is

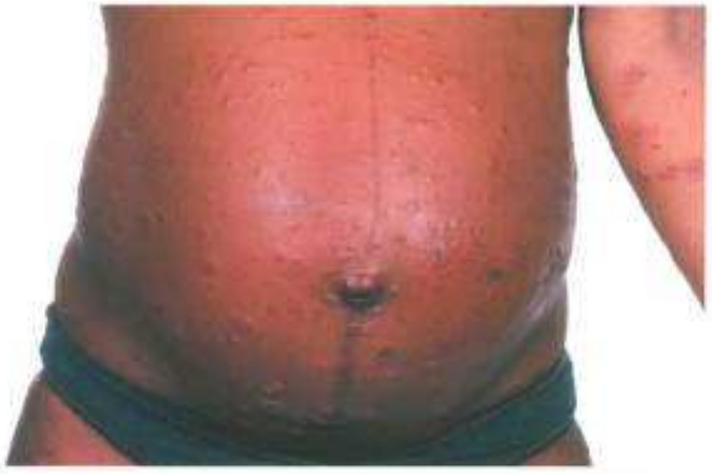


Fig. 28.12 Pemphigoid gestationis. Itchy, polycyclic, urticarial papules and wheals commence around the umbilicus, usually in the second trimester, and recur in successive pregnancies.

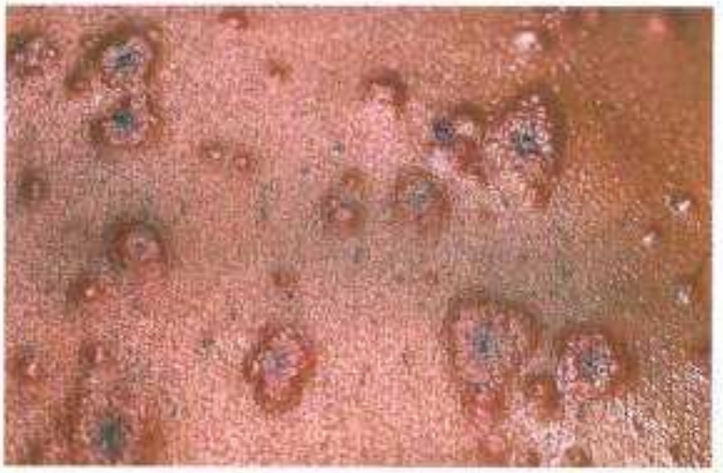


Fig. 28.13 Pemphigoid gestationis. This close-up photograph of the patient in Fig. 28.10 shows many vesicles of various sizes and polycyclic shapes. The condition is intensely itchy.

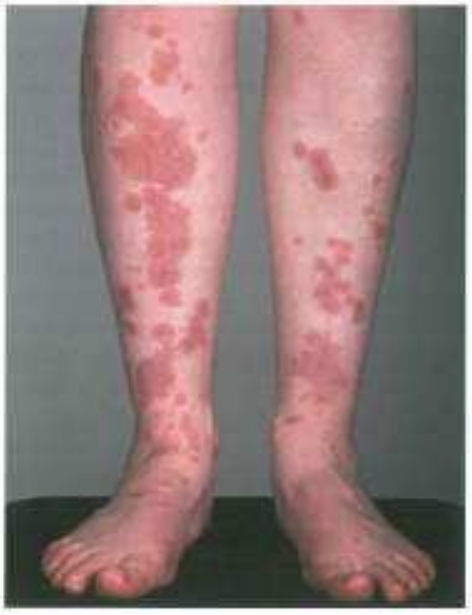


Fig. 28.14 Pemphigoid gestationis. Further wheals and very itchy blisters soon become visible on the limbs. It is identical clinically to bullous pemphigoid. C_3 and sometimes IgG is deposited at the lamina lucida. BP 180 is the target antigen.

Fig. 28.15 Immunofluorescence of pemphigoid gestationis. A brilliant linear blue/green band of C3 is illuminated by immunofluorescence at the basement membrane and is positive in all patients.

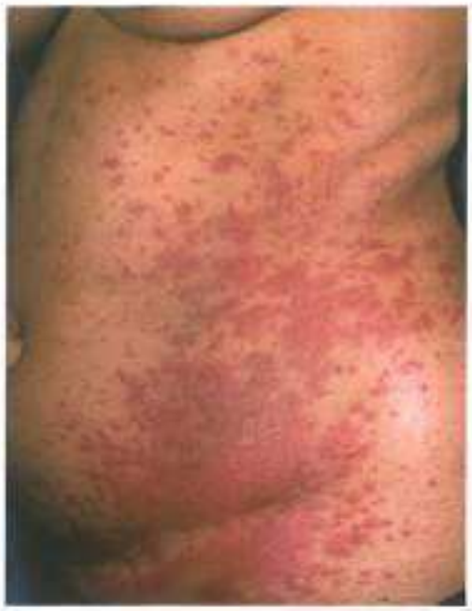


Fig. 28.16 Autoimmune progesterone dermatitis. The eruption, which may be eczematous, urticarial or simulate erythema multiforme, is recurrent around menstruation and may be reproduced by synthetic progesterone.

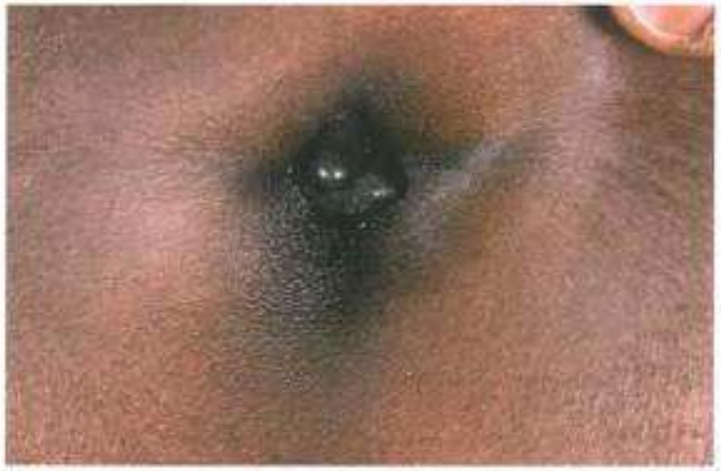


Fig. 28.17 Endometriosis. Direct implantation of endometrial tissue may occur in the skin; the diagnosis is confirmed histologically. There is a nodule that is tender or bleeds during menstruation.

doubt about this. Systemic steroids appear to be safe. Remission usually occurs 2–3 weeks after birth. There may be exacerbations with menstruation or oral contraceptives. Secondary sepsis should be treated with oral antibiotics. Occasionally the fetus is born with blisters from transplacental passage of antibodies but these disappear within 3 weeks.

Menstruation

Disorders reported as being exacerbated by menstruation include psoriasis, eczema, rosacea, lupus erythematosus, erythema multiforme, herpes simplex, aphthous ulcers and acne. The last may be due to the rise in progesterone following ovulation and formation of the corpus luteum prior to its withdrawal with oestradiol, which results in menstruation. *Autoimmune progesterone dermatitis* (Fig. 28.16) has a varied clinical appearance (eczema, urticarial or erythema multiforme-like) and is associated with the premenstrual period. It can be confirmed by measuring progesterone levels and correlating them with the intensity of the eruption. Skin testing is erratic. It may be exacerbated with progesterone. Autoantibodies are sometimes present. It may respond to estrogen or tamoxifen, but is best managed by a gynaecological endocrinologist.

Endometriosis may implant in the skin as firm bluish nodules (Fig. 28.17), which are uncomfortable or bleed during menstruation.

After the climacteric, the skin becomes dry; the epidermis is thin and there is loss of dermal elasticity. There is an atrophic vulvovaginitis and hot flushes are commonplace. Estrogens used for hormonal replacement therapy may result in melasma, spider angiomas and other effects. Progestogens may cause acne. *Keratoderma climactericum* on the palms and soles (which also occurs in men) may be related to obesity rather than the menopause.

The vulva and surrounding skin

Many skin disorders may involve these areas and are described throughout the book. The commonest that present and are symptomatic in the area are:

- **Inflammatory** Seborrhoeic eczema (Figs 28.18 and 3.64), lichen simplex (Figs 28.19 and 3.88), napkin dermatitis, psoriasis, lichen

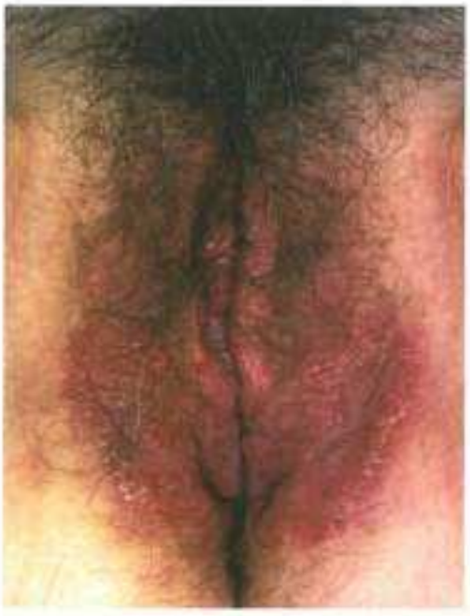


Fig. 28.18 Eczema. Eczema is common. This is seborrhoeic dermatitis, but patch tests were necessary to exclude contact dermatitis from a topical allergen. It responded to a potent steroid.

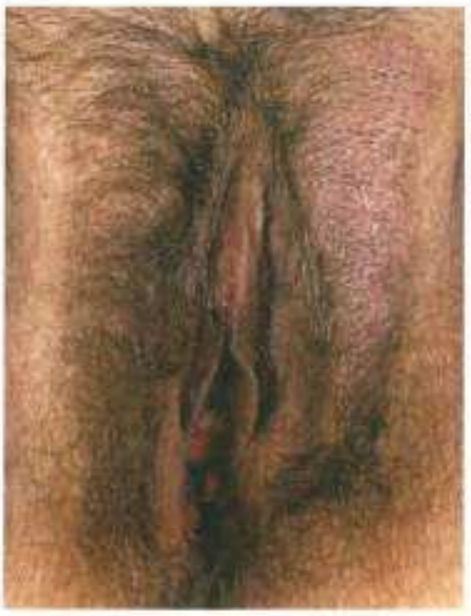


Fig. 28.19 Lichen simplex. This intensely itchy rash on the left side of her vulva is well defined and lichenified. It results from chronic scratching precipitated by anxiety or depression. It responds to superpotent steroids.

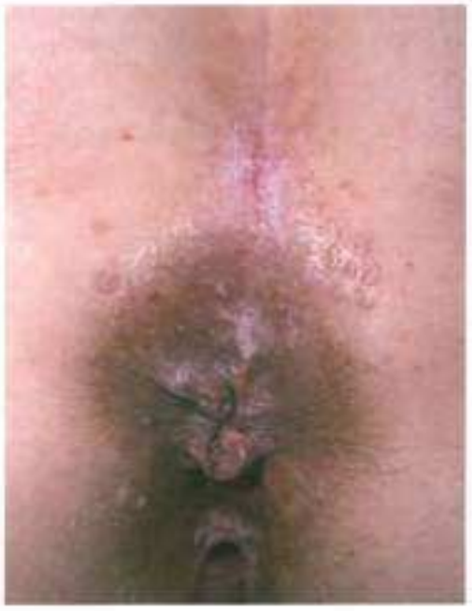


Fig. 28.20 Lichen planus. Very itchy, flat-topped, shiny, purple papules are present around the anus and vulva. Lichen planus may be limited to the mouth and genitalia or occur in these areas as part of a more widespread eruption. It responds to superpotent steroids.

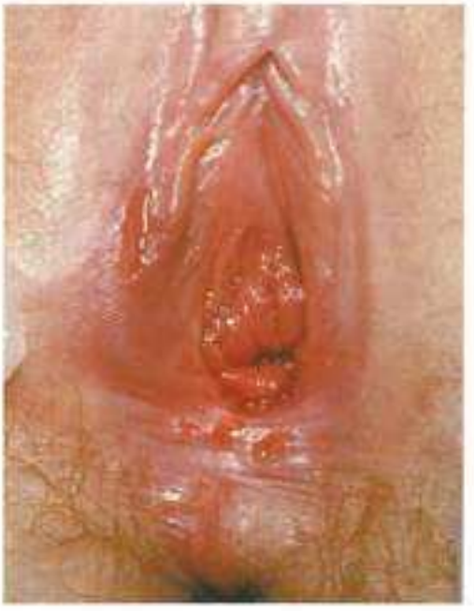


Fig. 28.21 Herpes simplex. Disorders that may be sexually transmitted, such as warts, syphilis, molluscum contagiosum and donovanosis, clearly affect the genitalia. Grouped vesicles are present just posterior to the vulva. Herpes simplex is a very common recurrent viral infection.

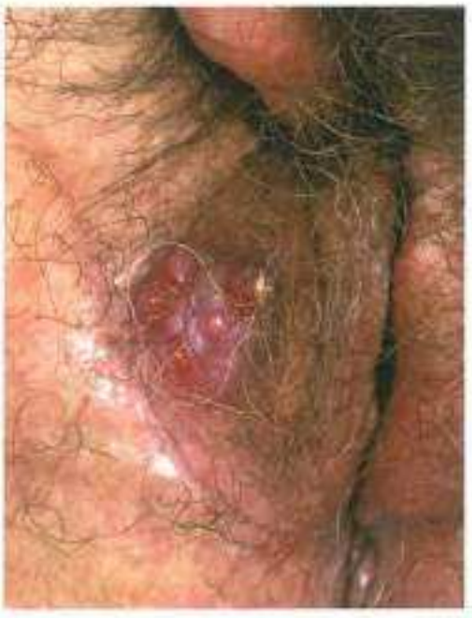


Fig. 28.22 Basal cell carcinoma. A lobulated pearly tumour with surface telangiectasia is present. Basal cell carcinomas do occur on the vulva but are rare. Bowen's disease and squamous cell carcinomas are much more common.

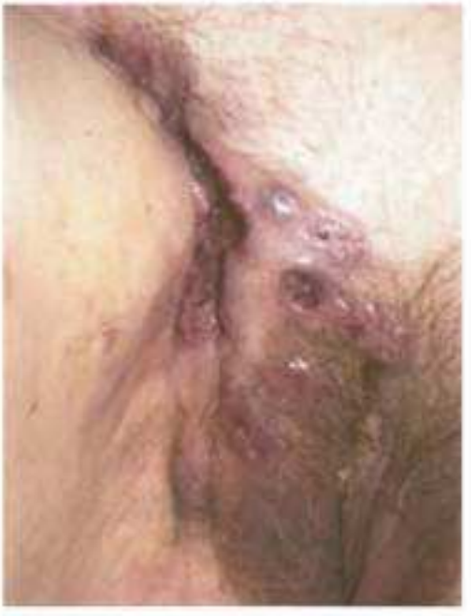


Fig. 28.23 Metastasis. There is an ulcerated plaque with nodules. Biopsy proved this to be a squamous cell carcinoma. The primary was found in the anus.

planus (Figs 28.20 and 7.33) and vulvovaginal gingival syndrome (Fig. 7.35).

- **Bacterial infection** Erythrasma and syphilis.
- **Viral infection** Herpes simplex (Figs 28.21 and 14.16), warts (Fig 14.62) and molluscum contagiosum.
- **Fungal infections** Candidiasis (Fig. 15.6) and tinea cruris.
- **Infestations** Pediculosis pubis (Fig. 16.23).
- **Cutaneous malignancies** Basal cell carcinoma (Fig. 28.22), Bowen's disease (Fig. 10.41), Squamous cell carcinoma (Fig. 10.67), malignant melanoma (Fig. 11.69), metastases (Fig. 28.23) and extramammary Paget's disease (Fig. 28.24).
- **Drugs** Steroid-induced striae.

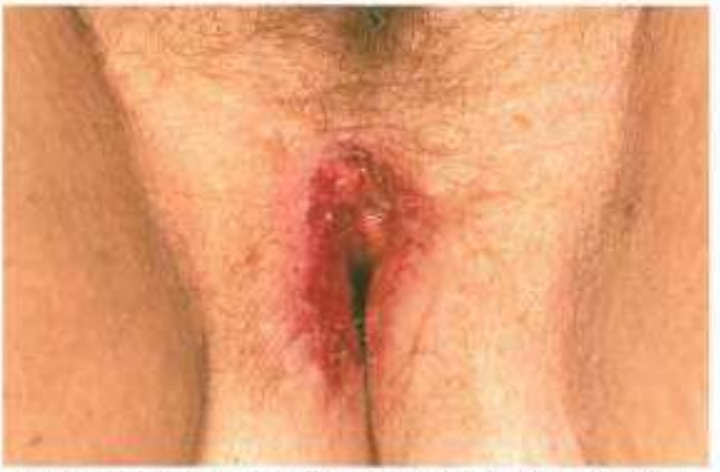


Fig. 28.24 Extramammary Paget's disease. The lesion is a very well-defined red plaque. Biopsy is critical for correct diagnosis.

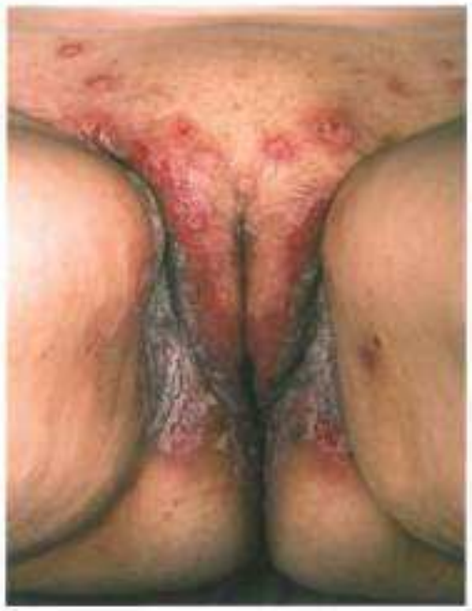


Fig. 28.25 Hailey–Hailey disease. The vulva and groin are covered in a vesicular eruption that has become confluent and macerated with a fissured surface posteriorly. A biopsy is necessary to demonstrate the lack of cohesion of the epithelial cells.

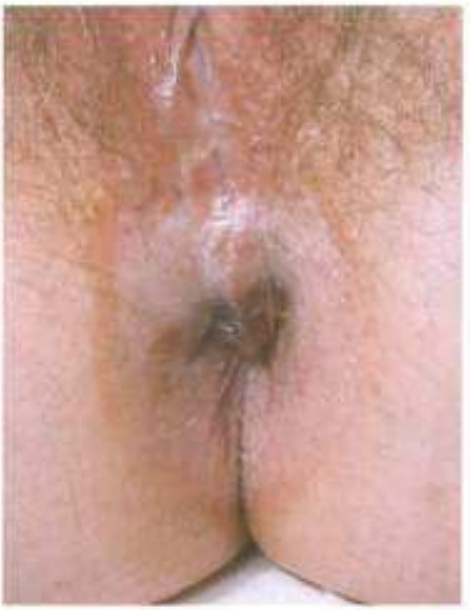


Fig. 28.26 Lichen sclerosus et atrophicus. Itchy, white, flat-topped lichenoid papules merge to form symmetrical sclerotic plaques, which become atrophic and sometimes haemorrhagic around the vulva and anus. Superpotent steroids are of great benefit.

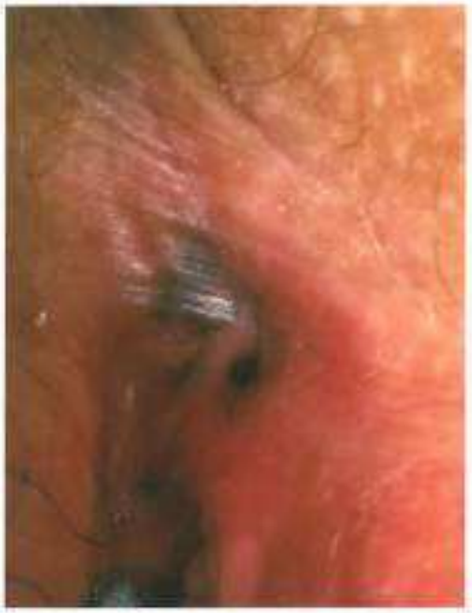


Fig. 28.27 Vulvovaginal melanosis. Acquired, brown, discoloured patches may occur on the genitalia. This is quite benign. Histologically, there is increased pigmentation but no atypia.

- **Developmental** Hailey–Hailey disease (Figs 28.25 and 20.57).
- **Immunological** Lichen sclerosus et atrophicus (Fig. 28.26), pemphigus and chronic bullous disorder of childhood (Fig. 19.64).
- **Hair** Alopecia areata.
- **Pigmentation** Vulvovaginal melanosis (Fig. 28.27).
- **Systemic disease** Pyoderma gangrenosum and Behçet's disease.

Skin disorders affecting the nipple and breast

The commonest conditions are:

- **Eczema** (Figs 28.28 and 28.29)

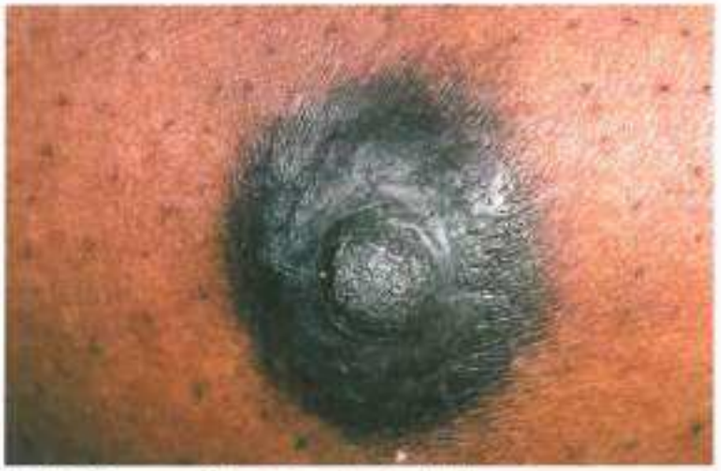


Fig. 28.28 Eczema of the nipple and areola. This is an uncommon manifestation of atopy. It is not as well defined as Paget's disease and may spread onto the breast. A biopsy is indicated if there is any doubt.

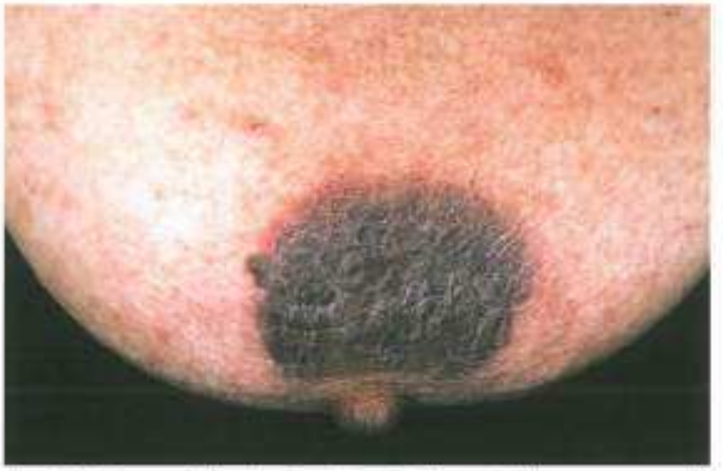


Fig. 28.29 Eczema of the nipple and areola. The area is itchy, may weep and is slightly raised and scaly. The other breast may also be involved.

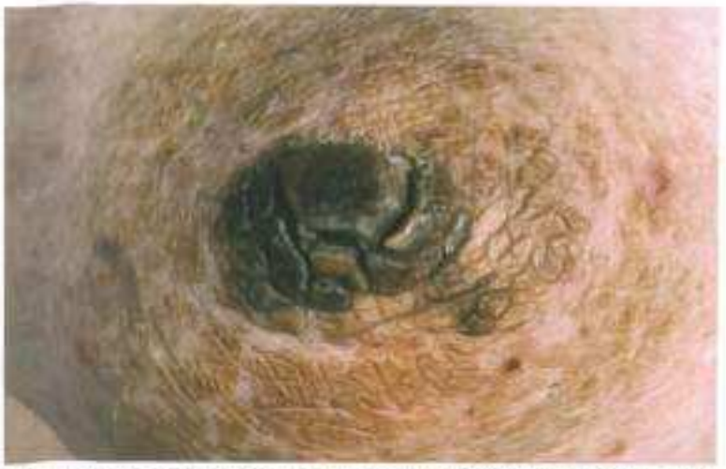


Fig. 28.30 Naevoid hyperkeratosis of the nipple. There is a warty (verrucous) hyperplasia of the nipple and areola. It is quite benign, but uncommon.

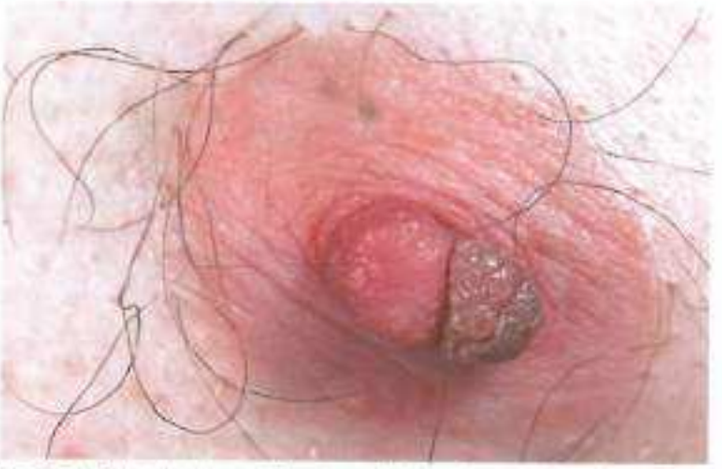


Fig. 28.31 Seborrhoeic wart. There is a well-defined papule with a fissured surface adjacent to the nipple.

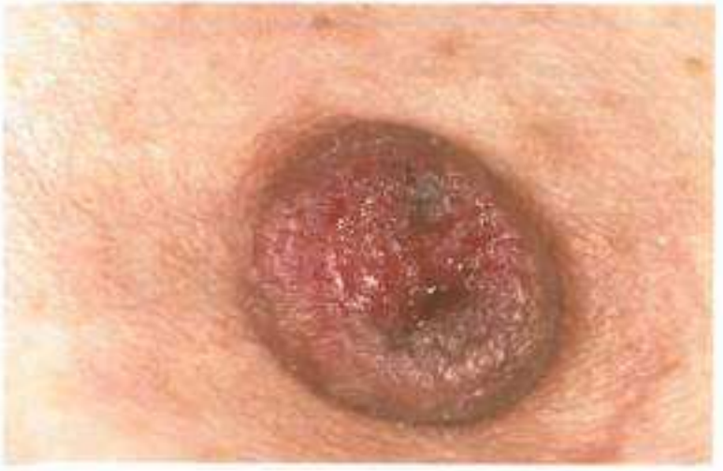


Fig. 28.32 Paget's disease of the nipple. There is an eroded, well-defined plaque on one nipple only. Biopsy is mandatory. It is associated with an intraductal carcinoma of the breast. It may spread beyond the nipple to involve the areola and surrounding skin.

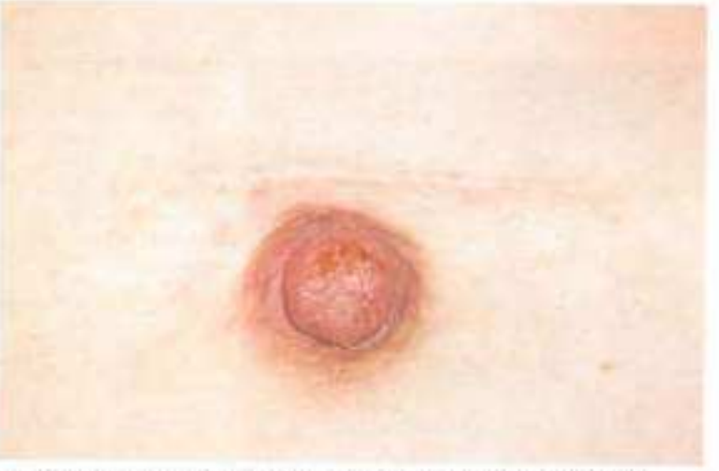


Fig. 28.33 Papillary adenoma of the nipple. This is a rare benign eroded tumour of the lactiferous ducts. It simulates Paget's disease but is confined to the nipple. The diagnosis is made histologically following excision. It is also called erosive adenomatosis.

- **Naevoid hyperkeratosis of the nipple** (Fig. 28.30)
- **Basal cell papilloma** (Fig. 28.31)
- **Paget's diseases of the nipple** (Fig. 28.32)
- **Papillary adenoma of the nipple** (Fig. 28.33)
- **Invasive carcinoma of the breast** (Fig. 28.34)
- **Metastatic disease** (Fig. 28.35)
- **Mycosis fungoides** (Fig. 28.36)
- **Skin cancer** (Figs 28.37 and 28.38)
- **Morphoea** (Fig. 28.39)
- **Accessory nipple** (Fig. 28.40)
- **Artefact** (Fig. 29.12)

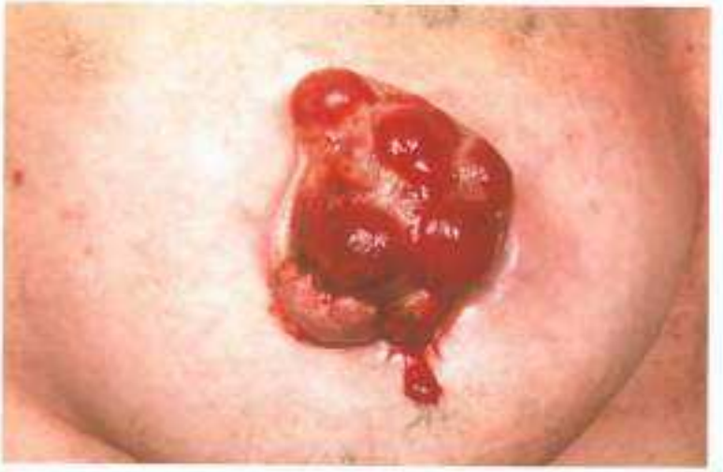


Fig. 28.34 Invasive carcinoma of the breast. There is a lobulated, red, nodular tumour. This may have commenced as Paget's disease but had been neglected.

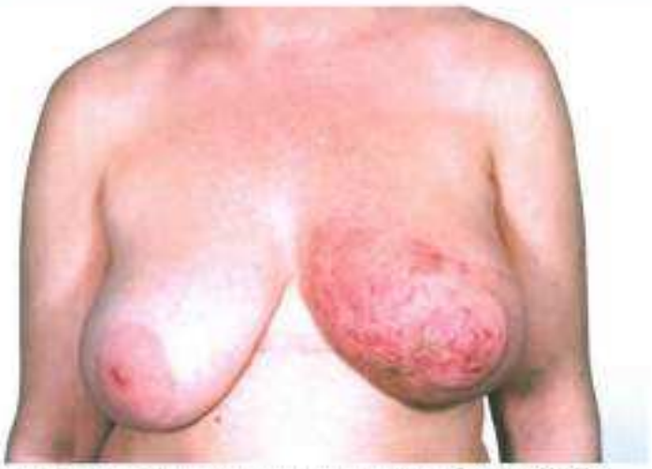


Fig. 28.35 Metastatic adenocarcinoma of the breast. There is a localized plaque of infiltrated red skin involving the breast and nipple. A skin biopsy confirmed localized metastatic spread of adenocarcinoma of the breast.

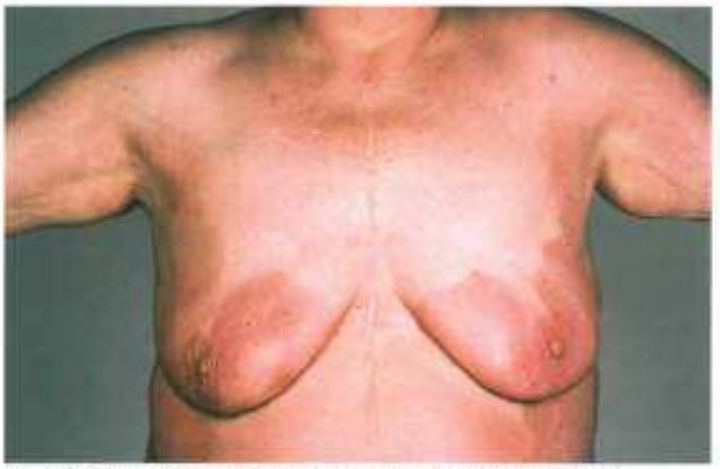


Fig. 28.36 Mycosis fungoides of the breast. The breast is commonly involved in cutaneous T cell lymphoma. There are severe patches that are pink, poikilodermatous and well defined with irregular margins.

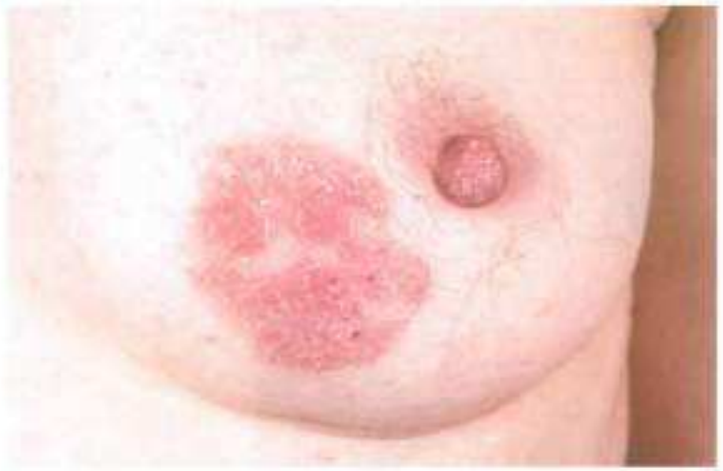


Fig. 28.37 Superfical basal cell carcinoma of the breast. The lesion is solitary and well defined. A fine, pearly margin to the red plaque is usually visible.

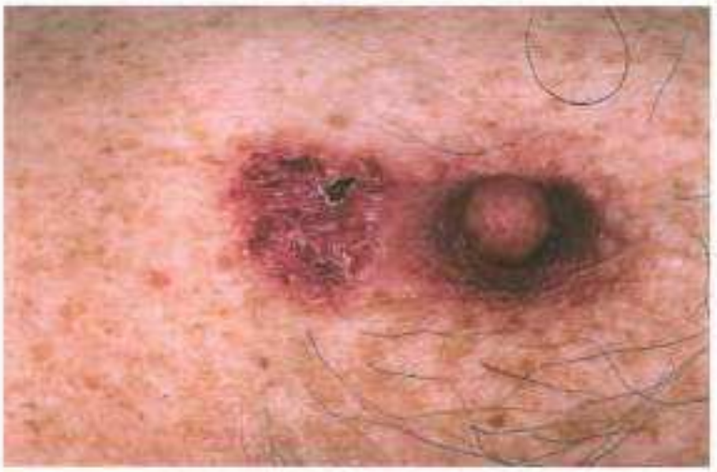


Fig. 28.38 Basal cell carcinoma. There is a very well-defined red plaque with a small scab adjacent to this man's nipple. Biopsy proved it to be a superficial basal cell carcinoma.

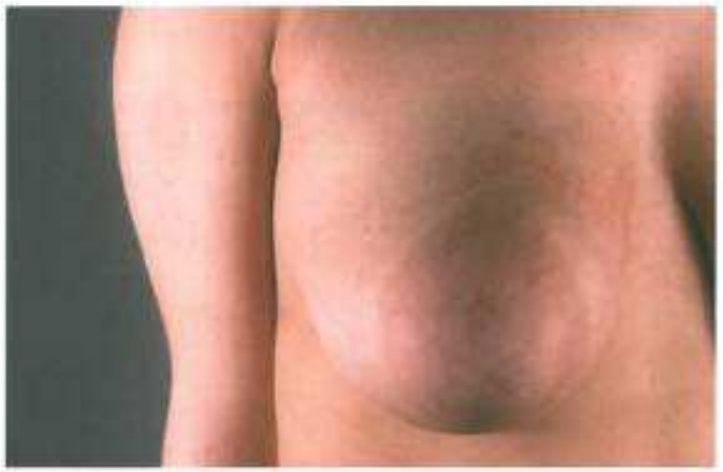


Fig. 28.39 Morphoea of the breast. There is tethering and hardening of the skin producing a localized form of scleroderma. The breast is a common site.

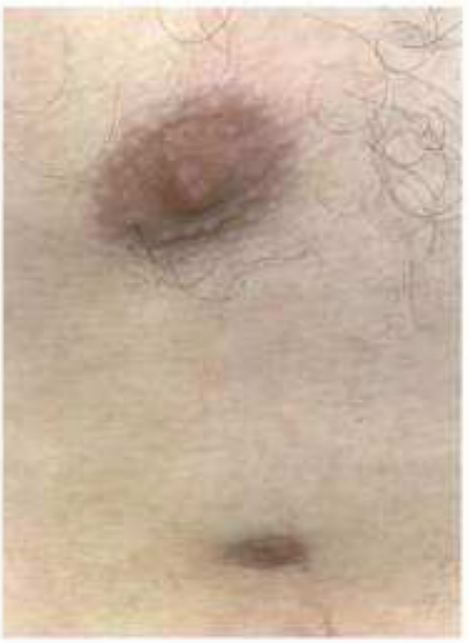


Fig. 28.40 Accessory nipple. This is common. It has the appearance of a very small nipple and may be bilateral. It occurs anywhere along the embryological milk line from the anterior axillary fold to the inner thigh.

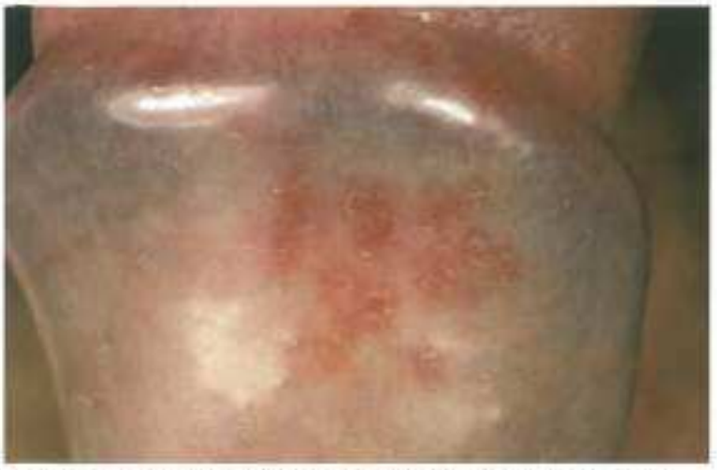


Fig. 28.41 Eczema. Contact dermatitis to rubber in condoms does occur but seborrhoeic eczema is more common and is often associated with alcohol misuse.

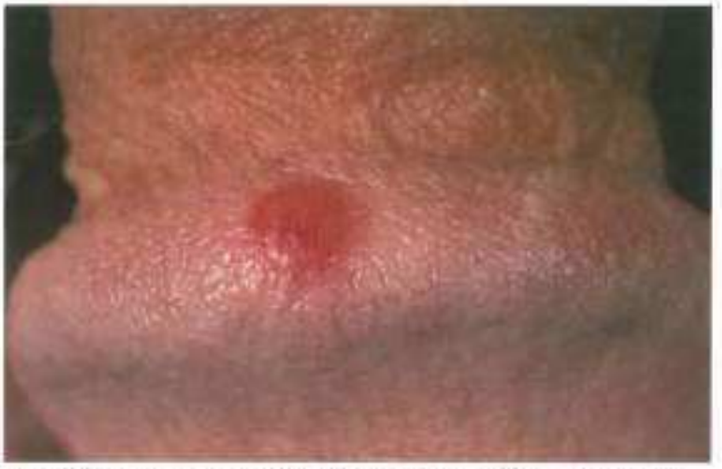


Fig. 28.42 Psoriasis. Psoriasis is common and may be the only manifestation other than involvement of the scalp. It is a deep red colour, slightly raised and well defined. Scaling may be absent.

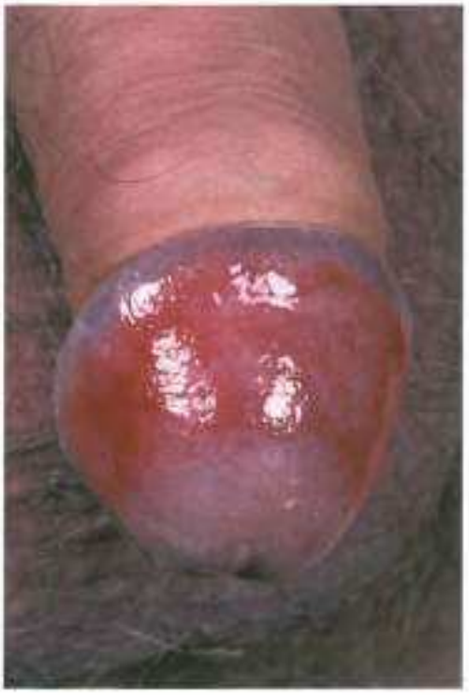


Fig. 28.43 Zoon's plasma cell balanitis. The area is a deep red colour and has a glazed appearance. It only occurs in the uncircumcised. Histopathology shows a striking plasma cell infiltrate. It responds temporarily to topical steroids and permanently to circumcision.

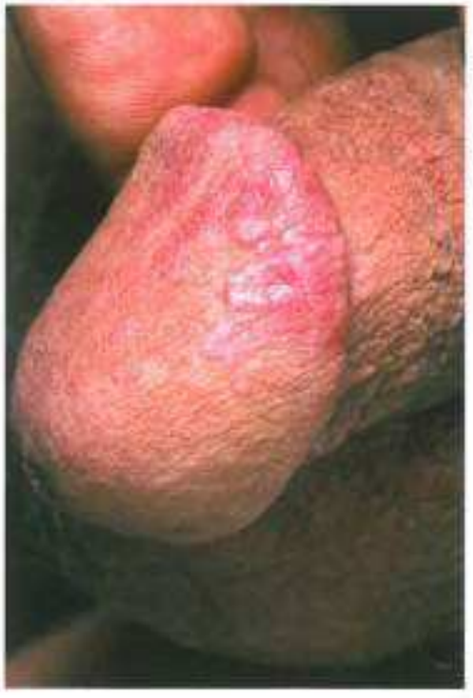


Fig. 28.44 Lichen planus. There are flat-topped shiny purple papules, which have partly become confluent on the glans penis, a common site for lichen planus. There are usually also lesions in the mouth.

Differential diagnosis of penile conditions

The common disorders affecting the male genitalia are:

- **Inflammatory**
  - **Eczema** (Fig. 28.41)
  - **Psoriasis** (Fig. 28.42)
  - **Plasma cell balanitis of Zoon** (Fig. 28.43)
  - **Lichen planus** (Fig. 28.44)
- **Benign tumours**
  - **Pearly penile papules** (Fig. 9.103)
- **Cutaneous neoplasms**
  - **Bowenoid papulosis** (Fig. 10.43)
  - **Squamous cell carcinoma** (Fig. 28.45)
  - **Bowen's disease** (Fig. 10.40)
- **Bacterial infections**
  - **Syphilis** (Fig. 13.55)

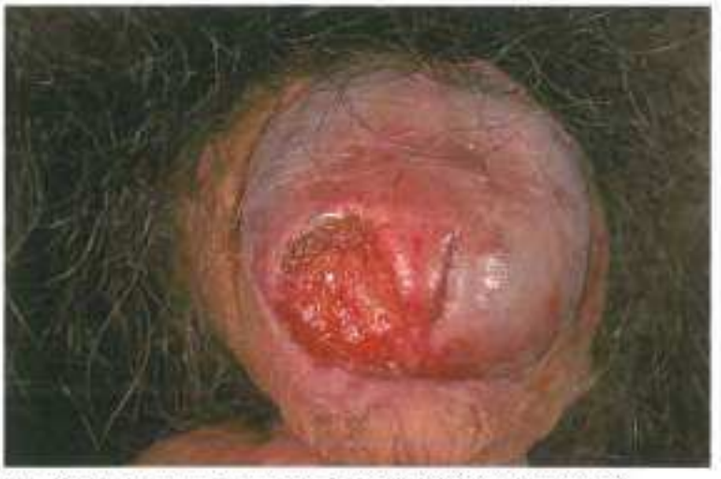


Fig. 28.45 Carcinoma of the penis. The nodule has become ulcerated. Squamous cell carcinoma does not occur in males circumcised in infancy.

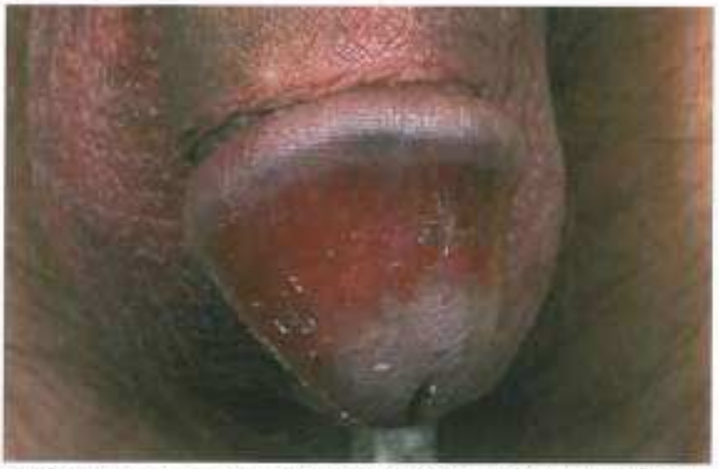


Fig. 28.46 Kaposi's sarcoma. There is a well-defined, red plaque. The lesion is quite characteristic of human immunodeficiency virus infection.

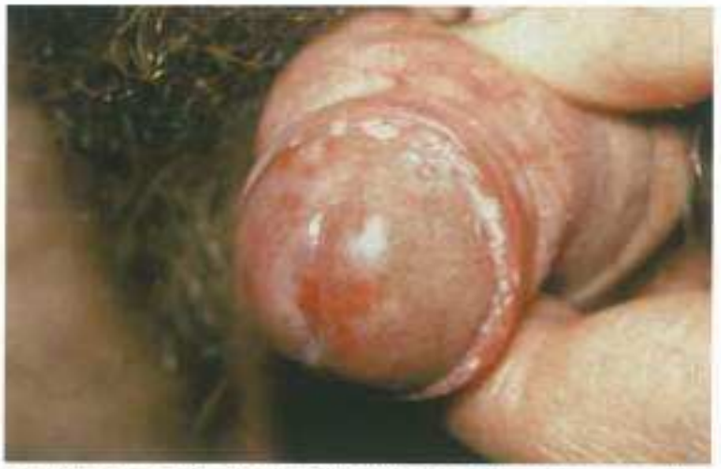


Fig. 28.47 Candidiasis. Creamy white pustules occur. It is most common in the uncircumcised and may be a presentation of diabetes mellitus.

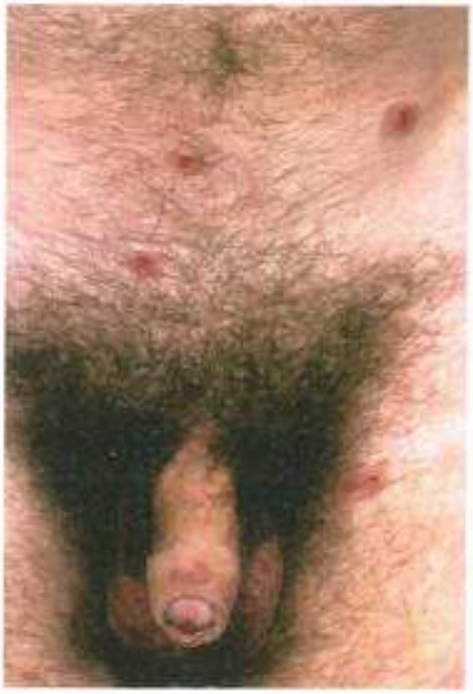


Fig. 28.48 Scabies. Nodules may persist on the genitalia for many weeks after the disease has been treated.

- **Viral infection**
  - **Herpes simplex** (Fig. 14.20)
  - **Warts** (Fig. 14.61)
  - **Molluscum contagiosum** (Fig. 14.51)
  - **Kaposi's sarcoma** (Fig. 28.46)
- **Fungal infection**
  - **Candidiasis** (Fig. 28.47)
- **Infestation**
  - **Scabies** (Figs 16.10 and 28.48)
  - **Schistosomiasis**
- **Tropical venereal**
  - **Chancroid** (Fig. 13.83)
  - **Donovanosis** (Fig. 13.86)
  - **Lymphogranuloma venereum** (Fig. 13.84)
- **Drugs/reactive**
  - **Fixed drug eruption** (Fig. 28.49)
  - **Erythema multiforme** (Fig. 18.10)
- **Autoimmune disorders**
  - **Pemphigus** (Fig. 28.50)

Fig. 28.49 Fixed drug eruptions. Blistering resulting in erosions is a striking manifestation of the fixed drug eruption, in this case caused by a sulphonamide. It recurs at the same site if the drug is encountered again.

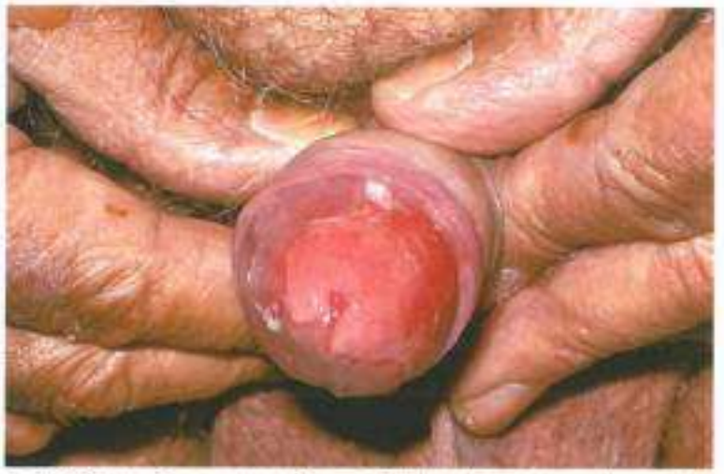


Fig. 28.50 Pemphigus vulgaris. Raw, painful, denuded erosions on the genitalia may be the first sign of pemphigus. (Courtesy of the Institute of Dermatology.)

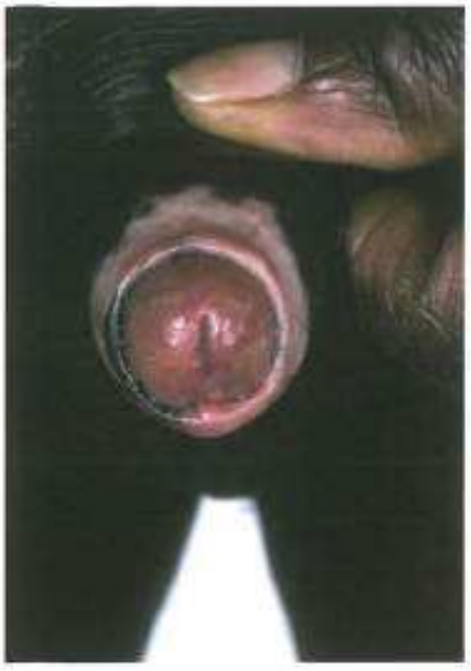


Fig. 28.51 Vitiligo. The total absence of pigment results in a striking symmetrical white colour of the skin.

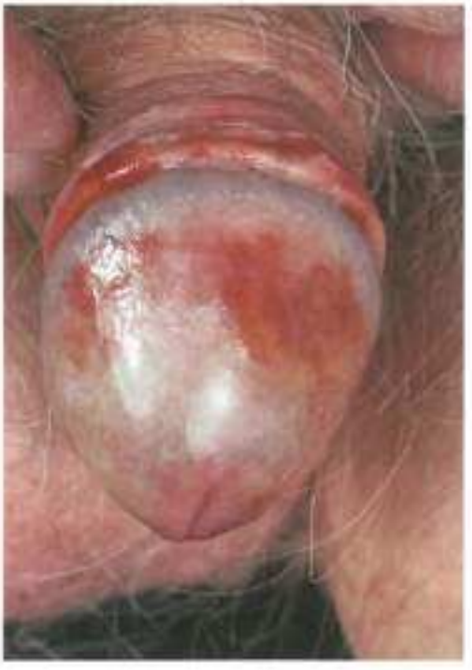


Fig. 28.52 Lichen sclerosus et atrophicus. There is a white, sclerotic background with atrophy resulting in spontaneous purpura. There may be meatal stenosis and difficulty retracting the foreskin. Superpotent steroids have revolutionized treatment.

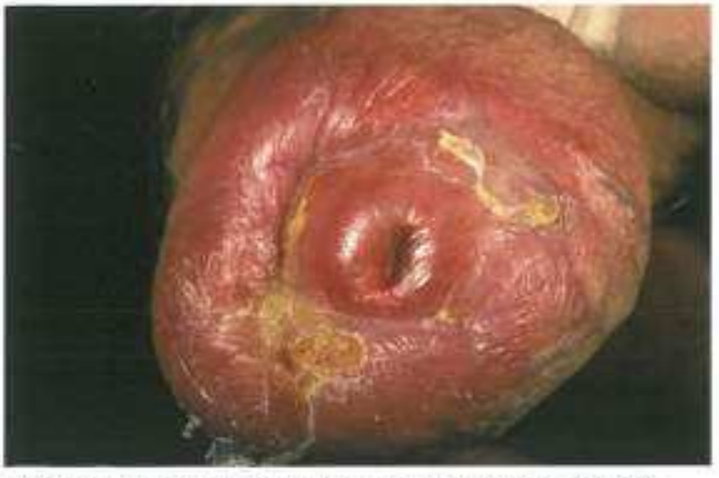


Fig. 28.53 Micaceous and keratotic pseudoepitheliomatous balanitis. The glans becomes covered with mica (asbestos-like) scales and horny crusts. It is uncommon but benign. There is a pseudoepitheliomatous histology. It may be a variant of lichen sclerosus.

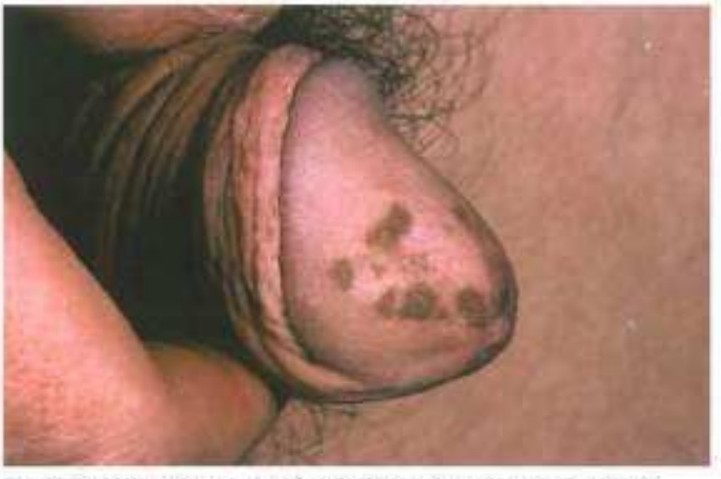


Fig. 28.54 Melanotic macules. Acquired hyperpigmented macules are not uncommon and are not significant.

- **Vitiligo** (Fig. 28.51)
- **Lichen sclerosus et atrophicus** (Fig. 28.52)
- **Micaceous and keratotic balanitis** (Fig. 28.53)

- **Pigmentary**
  - **Melanotic macules** (Fig. 28.54)
- **Systemic disorders**
  - **Behçet's disease** (Fig. 22.134)
  - **Reiter's syndrome**
- **Psychological causes**
  - **Dermatitis artefacta.**

Psychological disorders of the skin 29

Some patients with cutaneous symptoms have underlying psychological problems such as anxiety, depression, obsessive-compulsive disorder or psychosis. They may present in various ways. It is particularly helpful to have a liaison psychiatrist working with a skin department. Patients are much more willing to accept referral to one in such a venue and be managed jointly with a dermatologist than go to a psychiatric department.

Appropriate reactions

It is natural that a patient should be anxious or depressed regarding a disfiguring condition, such as acne or psoriasis. He or she may feel embarrassed or even 'leprous' and have difficulty in making satisfactory relationships. The patient may be withdrawn, introverted or aggressive as a result. The degree of involvement of the skin is no guide to the degree of unhappiness. Mild psoriasis may be devastating to one patient whereas severe disease may be borne with good humour and tolerance by another, but most would give a lot to be free of it. Clearly, sympathy, understanding, compassion and a desire to help are important, but they are not always forthcoming from doctors more accustomed to serious medical disorders.

Overconcern regarding minor blemishes

Symptoms that involve the skin are common presentations of anxiety and depression. In particular, patients complain of or are anxious about minor conditions or blemishes, such as mild seborrhoeic dermatitis, haemangiomas and seborrhoeic warts. If these patients were happy, the lesions would merit no concern, but in the distressed they assume a disproportionate importance. The patients are usually middle-aged and are either depressed because of marital failure or anxious because of excessive pressure and stress at work.

Lack of abnormal physical signs

Affective disorders may also present as complaints for which no abnormal physical signs may be found on examination. This is sometimes known as dermatological non-disease. It includes a group who are suffering from *dysmorphophobia*, a rare and serious disorder in which the patient, usually female, is convinced that there is something wrong with their face. The condition is not amenable to reason and is thus a delusion. It is very difficult to treat and may end in suicide. Much more commonly, however, patients have less-severe forms that respond to psychological treatment but are sometimes perplexing to practitioners, who are taken in by the patient and believe that there must be something wrong with the skin, even though there is nothing abnormal to see. The common symptom complexes are referable to various parts of the body.

- **The scalp** The patient may complain of excessive itching or burning of the scalp or, in females in particular, of excessive hair loss. In the former, the scalp appears quite normal on examination. In the latter, there may be abundant or acceptable amounts of hair and no adequate explanation, such as telogen effluvium, for the 'loss'. Depression and unhappiness in personal relationships are usually the explanation.
- **The face** Burning is the most usual symptom – an unusual one in skin disorders, the exception being *erythropoietic protoporphyria* – and should alert the practitioner. Complaints regarding redness of the face are common too, even when there is none to be seen.
- **The genitals in males** The male patient may become preoccupied with the penis or scrotum. He describes irritation of the scrotum and redness of the glans or corona, particularly during an erection, and may find intercourse painful. He tends to examine the penis regularly and conscientiously and describes the abnormality in a painstaking manner (*penile preoccupation*). The condition is invariably diagnosed and treated as thrush and yet there are no real abnormal physical signs, apart from possibly minimal erythema. The patient usually receives a multiplicity of topical remedies but none are effective because the patient requires counselling. Marital disharmony, sexual inexperience, stress and depression are the most common causes.
- **The genitals in females** The complaint is usually of symptoms referable to the vulva without any abnormality on examination. In previous generations, itching (*pruritus vulvae*) was the symptom; however, for some reason, this has been replaced by burning (*vulvodynia*). The discomfort (*chronic vulval discomfort*) may interfere with walking and sitting and certainly precludes sexual intercourse. The condition is often persistent and extremely difficult to treat, the patient consulting many doctors unsuccessfully and being reluctant to accept psychiatric help.
- **The eyelids** The patient, usually female, complains of irritation of the eyelids. The symptoms will usually have already baffled several doctors, including ophthalmologists, who can find nothing wrong but suspect an allergic cause. It is the lack of abnormal physical signs on examination of the skin of the eyelids that should alert the practitioner. The itchy eyelid syndrome possibly represents a suppression of the need to weep and display pent-up unhappiness. Often the patient will readily recount problems if challenged.
- **The mouth** *Glossodynia* is quite a common symptom of depression. The patient complains of burning or soreness in the mouth, particularly of the tip of the tongue, and may describe abnormalities such as blisters or ulcers, but there is never anything to see and blood tests are normal. The patient is usually diagnosed as having thrush or an allergy to dentures, but treatment is of no avail unless the psychological nature of the condition requires recognition. It may respond well to counselling and low-dose antidepressants, such as amitriptyline 25 mg at night.
- **The anus** *Pruritus ani* is a common disorder, especially in males. Although many explanations are given for the intense irritation, for example anal sphincter dysfunction, anal tags, fissures, haemorrhoids, faecal soiling and thus 'allergy' to bacterial endopeptidases, a psychological disorder is more probable. There are no abnormal physical signs on examination and the condition is remarkably chronic and resistant to all manner of therapies. Certainly by the time a dermatologist is consulted, the patient will bring an accurate list (most unusual for

other skin conditions) of numerous medications that have been tried unsuccessfully. The patient is usually introspective, obsessional and mildly hypochondriacal and will describe the malady in intimate detail. It does not respond well to psychological measures. It is wise, however, to avoid medicaments that contain antibiotics, anaesthetics and other potential allergens because dermatitis medicamentosa (Fig. 29.1) may result.

- ***Notalgia paraesthetica*** This is a condition of itching limited to the medial side of the scapula. There may be nothing to see or pigmentation (Fig. 29.2) secondary to rubbing and scratching. It may respond to topical capsaicin, so may have a neurological rather than psychological basis.
- ***Trigeminal neuralgia* (tic douloureux)** There are recurrent paroxysms of stabbing or burning pain unilaterally in one or more of the sensory divisions of the trigeminal nerve, possibly due to demyelination of the nerve as a disease process such as disseminated sclerosis, vascular compression of the trigeminal root or without obvious cause. Carbamazepine, gabapentin or baclofen gives relief in most patients.

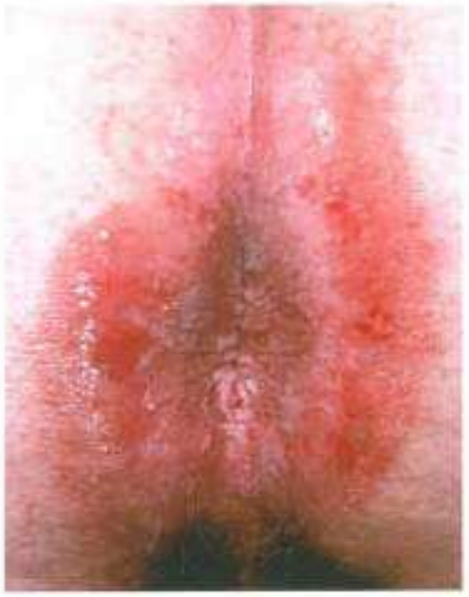


Fig. 29.1 Dermatitis medicamentosa. This man had suffered from pruritus ani for many years. There was never any abnormality on examination until he developed a contact dermatitis to one of his medicaments.

Phobias

The other variety of psychological skin disorder with no physical abnormality is the phobia. Venereophobia manifests itself in different ways depending on the diseases that are in the news at the time. Syphilis was the standard until it was superceded by herpes genitalis in the 1970s and replaced now by the acquired immunodeficiency syndrome (AIDS). Clearly, the patient may have good reason to fear these disorders, but in true venereophobia the patient is not at risk at all but is severely depressed, and this should be recognized. The condition does not respond to reassurance but does respond to treatment of the depression. A rare and bizarre phobia is parasitophobia (delusional parasitosis).

DELUSIONAL PARASITOSIS

A firmly held but unfounded belief of infestation of the skin.

Aetiology

The patients are truly deluded in that they tenaciously hold the belief that they are infested and remain unconvinced even though medical examination of their clothing and skin refutes the point. By the time they reach the specialist, patients have been told by one or several doctors that they are not infested. They have usually changed doctors as a result. They often have called in the public health authorities to fumigate their homes and they will bring specimens to the consultation to prove the infestation. These specimens are usually scales of skin, not parasites.

Clinical Features

There are no abnormalities on the skin other than occasional scratch marks and certainly there are no parasites to be seen. The specimens that the patients bring with them usually indicate the diagnosis (Fig. 29.3).

Management

Parasitophobia is a true delusion, quite unamenable to reason, and should be recognized and treated as such. The parasitophobia is usually the only delusion (monosymptomatic hypochondriacal psychosis) and management centres around fully examining the patient, empathizing and acquiring enough of his or her confidence such that the patient takes the oral medication to eliminate the 'parasites' from within. The psychotropic drug pimozide can be helpful, but it may have extrapyramidal effects and prolongation of the QT interval. Other drugs used to treat

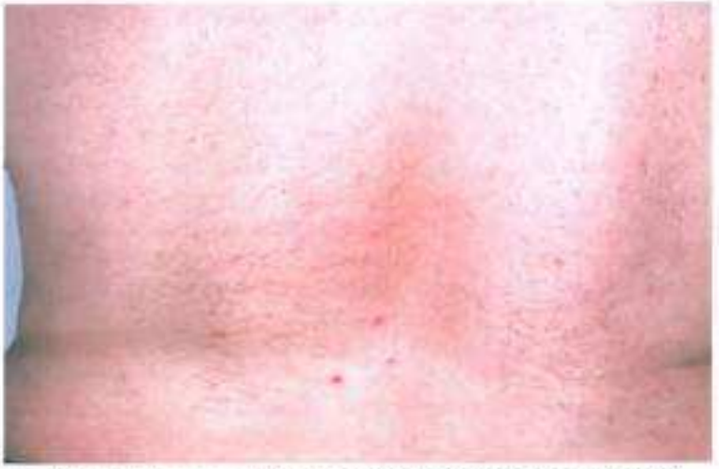


Fig. 29.2 Notalgia paraesthetica. It is a moot point whether this is a form of psychogenic pruritus, because it may respond to topical capsaicin. It occurs on the medial side of the scapula or sometimes lower. There may be nothing to see or just pigmentation secondary to rubbing.

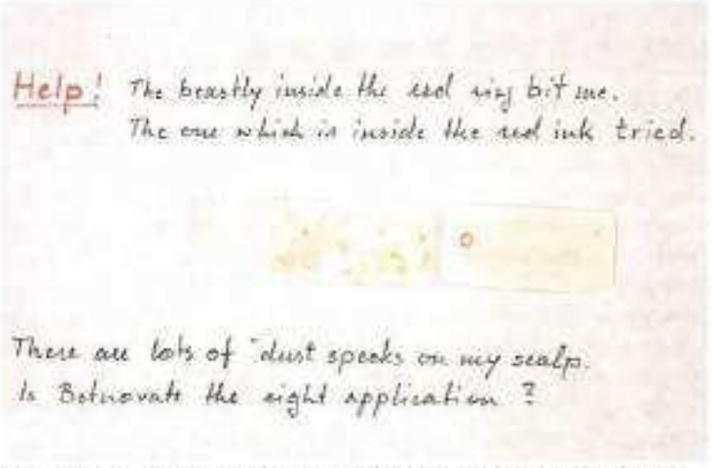


Fig. 29.3 Delusional parasitophobia. The specimens that patients bring with them are not parasites but scales of skin or extraneous material.

schizophrenia, such as risperidone or its main active metabolite paliperidone (5-HT_{2A} and D2 receptor blockers) may be helpful. Care must be taken with regard to interactions with other drugs which inhibit the P450 3A enzyme (macrolide antibiotics, protease inhibitors and azoles). In a significant number of patients, the delusion will pass, but other patients are singularly difficult to help. The suggestion of referral to a psychiatrist is usually greeted with antagonism, and it behoves the dermatologist to exercise considerable skill in its management.

Exacerbations of skin disorders by emotional factors

A number of skin disorders are made worse by 'life events'. For example, many patients observe that their psoriasis will deteriorate after a shock or when they are highly stressed, although clearly psoriasis is not a psychiatric disorder. Other conditions that are also affected in this manner are atopic eczema, alopecia areata, pompholyx, seborrhoeic eczema, herpes simplex, dermographism and chronic urticaria. It is always worth enquiring about the patient's personal life, including alcohol consumption, as simple counselling may frequently help the patient to cope with this exacerbation of their disorder while it is being treated with standard topical remedies.

Dermatoses with a psychological aspect

Some skin diseases have an accompanying component of psychological abnormality. Lichen simplex probably results from scratching or rubbing of the skin secondary to a minor affective disorder. However, it persists until treated with topical steroids, because the condition induced is eczematous and, therefore, pruritic in its own right.

Acne excoriée des jeunes filles (Fig. 29.4) may commence as a minor degree of acne, but ultimately the acne is non-existent and the abnormality has become a self-perpetuating and self-induced neurotic disorder.

Trichotillomania (Fig. 29.5) is a nervous habit tic for the most part, similar to biting the nails.

Picking at the skin may result in localized thickenings, often on the arm (Fig. 29.6) or hand. The thumbnail (Fig. 29.7) may be affected in a

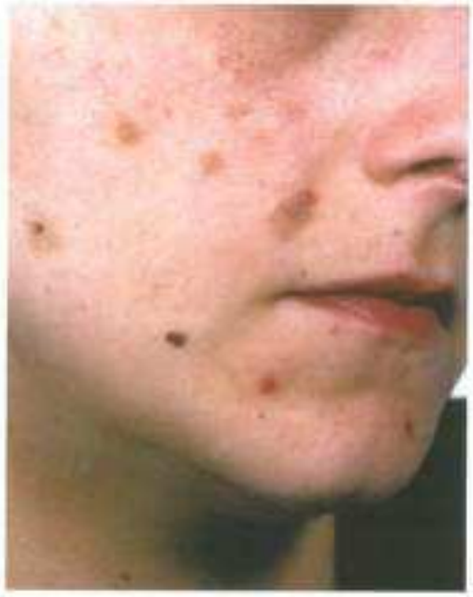


Fig. 29.4 Acne excoriée des jeunes filles. This woman picks at her skin and produces excoriations that result in unsightly postinflammatory pigmentation.

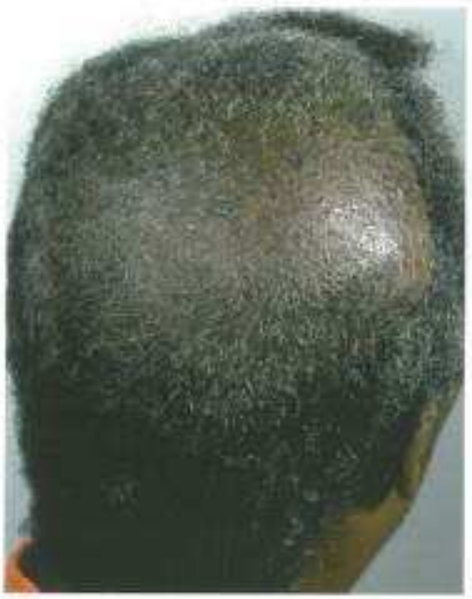


Fig. 29.5 Trichotillomania. This disturbed woman had broken off most of the hairs on the back and top of the scalp. The hair on the front of the scalp is intact. It is a form of obsessive-compulsive disorder.

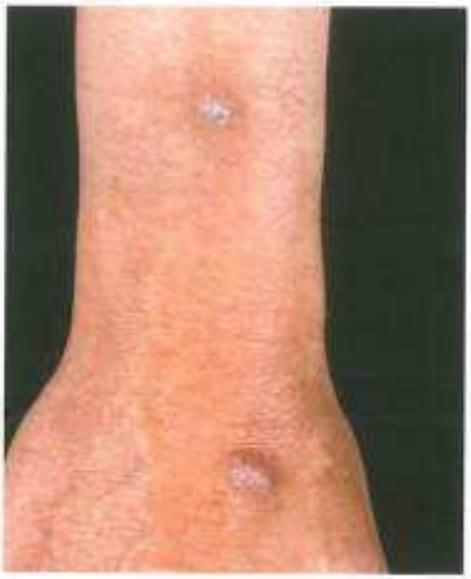


Fig. 29.6 Habitual picking at the skin. These two thickened nodules were the result of continuous picking at the skin. This habit tic is a manifestation of anxiety.

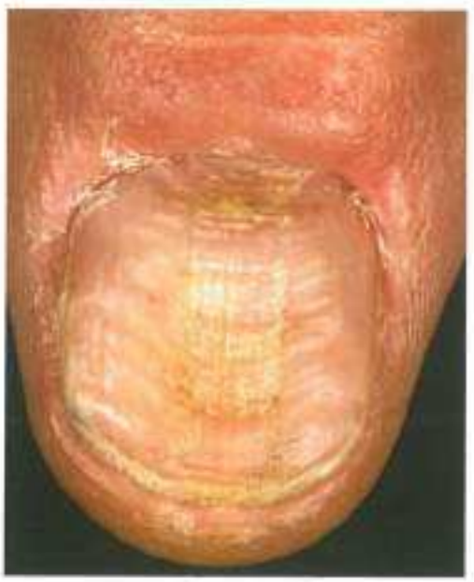


Fig. 29.7 Habitual picking at the nail. A ridge over the length of the thumbnail has resulted from the continuous running of the index fingernail along it and damage to the posterior nailfold.

similar way. There are other forms of habit tic. Neurotic excoriations are described below. Prurigo (Fig. 29.8) is a similar, very itchy disorder where there may be a strong psychological component to the scratching of the skin (see Ch. 22).

Trigeminal trophic syndrome is a form of self-mutilation triggered by abnormal sensations in the distribution of the sensory branch of the trigeminal nerve. The ulceration begins at the ala nasi (Fig. 29.9), spreading to the cheek and upper lip, but sparing the nasal tip (which is innervated by the external nasal branch of the exterior ethmoidal nerve). It is often iatrogenic (Fig. 29.10), following attempts to alleviate trigeminal neuralgia by ablating the gasserian ganglion, but may be caused by VZV HSV, mycobacteria, infarction of the posterior cerebellar artery or a cranial neoplasm. The differential diagnosis is basal cell carcinoma, nasal NK/T cell lymphoma and Wegener's granuloma.

Dermatitis artefacta is a rare disorder of mutilation of the skin that indicates deep psychological disturbance.

NEUROTIC EXCORIATIONS

An itchy condition, characterized by scratching or picking at healthy skin, where the underlying cause is anxiety.

Aetiology

Generalized excoriation is more common in women and is a demonstration of unhappiness. Localized picking at the skin is a mild form of neurosis.

Clinical Features

Symptoms

Irritation of the skin.

Morphology

Excoriations at various stages of development, with postinflammatory hyperpigmentation and scarring.

Distribution

It may be generalized, in which case the limbs and upper back are characteristically involved (Fig. 29.11), or localized (Fig. 29.12).

Fig. 29.8 Prurigo nodularis. There is intense irritation of the skin without any proven medical explanation. Continual scratching leads to excoriated nodules.

Management

Once a skin disorder or systemic explanation for the itching has been excluded, recognition and elucidation of the root of the psychological problem and its treatment is important. The lesions themselves may be treated with, for example, medicated bandages if the limbs are involved or topical steroids under occlusion so that the patient cannot scratch the skin. Doxepin, a powerful H_1 receptor antagonist as well as an antidepressant, is a powerful agent. It is however a tricyclic and may cause weight gain, postural hypotension, cardiac conduction irregularities and anticholinergic effects. Habit tic reversal is also a useful psychological tool used to break the itch-scratch cycle.

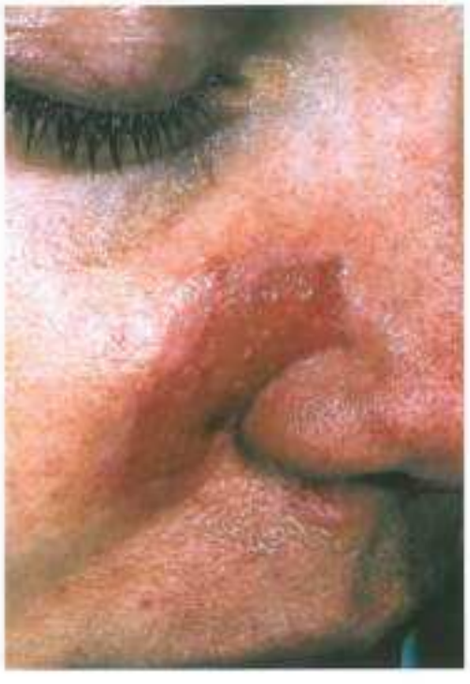


Fig. 29.9 Trigeminal trophic syndrome. There is ulceration at the ala nasi caused by self-mutilation. It is artefactual.

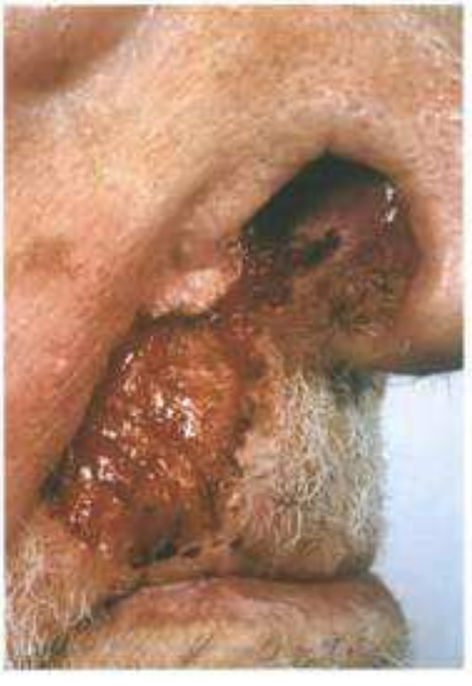


Fig. 29.10 Trigeminal trophic syndrome. There is extensive deep ulceration in the distribution of the sensory branches of the trigeminal nerve with sparing of the nasal tip, which is innervated by a separate nerve. This was caused by ablation of the gasserian ganglion.

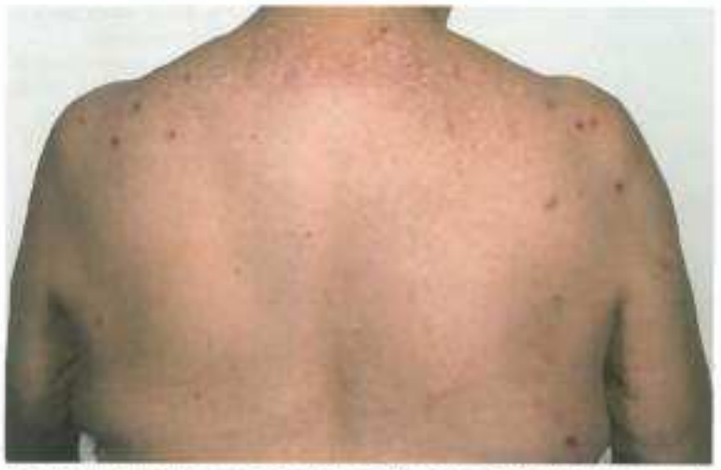


Fig. 29.11 Neurotic excoriations. This usually occurs in females and represents a chronic picking of the skin of the limbs and upper back, but sparing of the inaccessible mid-upper back skin, which results in scarring.

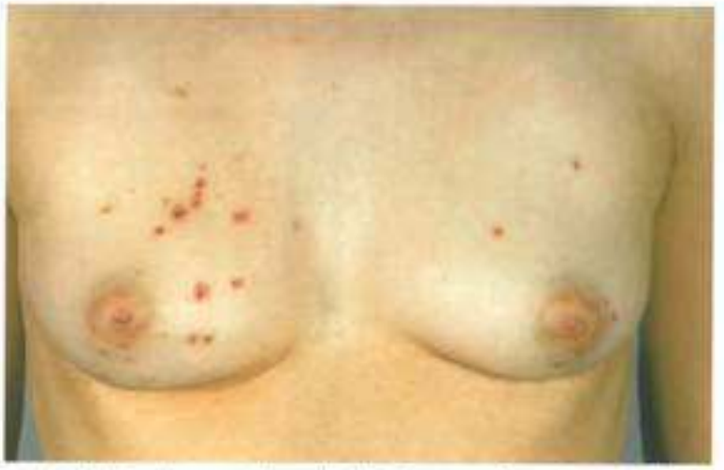


Fig. 29.12 Neurotic excoriations. In this instance, scratch marks were limited to the breast. The patient accepted psychiatric help and her anxieties were successfully treated. (Courtesy of St Mary's Hospital.)

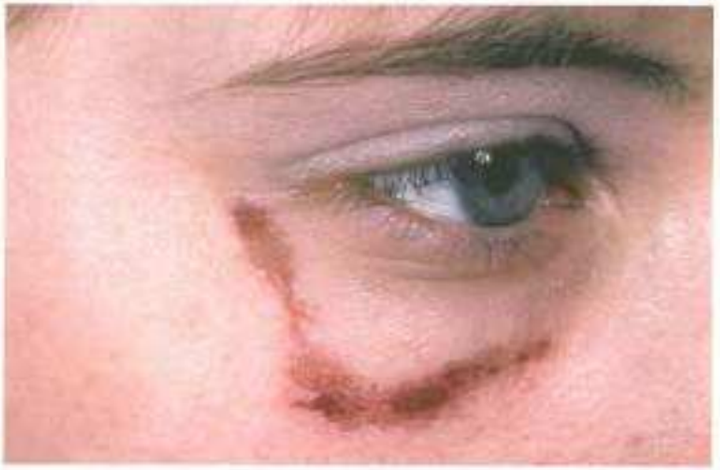


Fig. 29.13 Dermatitis artefacta. This shows the classic linear geometric pattern of artefact on the face.

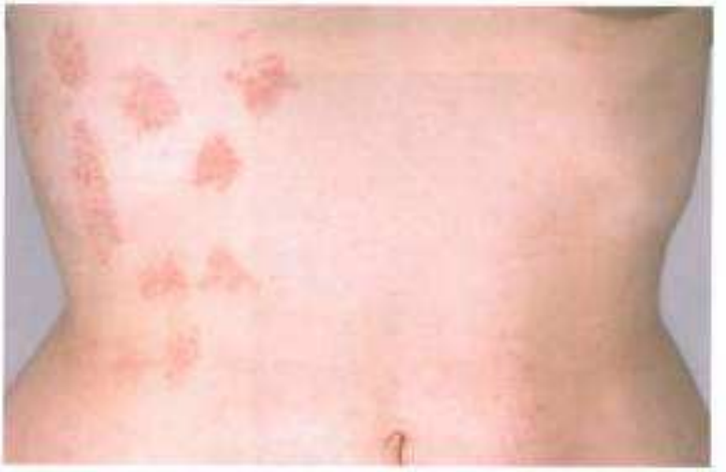


Fig. 29.14 Dermatitis artefacta. There are round and linear lesions on one side of the body from an attempt to simulate herpes zoster. (Courtesy of Prof. Hywel Williams.)

DERMATITIS ARTEFACTA

A mutilation of the skin induced, but not admitted to, by the patient.

Aetiology

The condition is rare. It is largely confined to females and is a little more common in the nursing profession. The patients show an indifference to the unsightliness of the damage to the skin. In some, the condition is a psychosis that is completely denied by the patient and is very difficult to treat. In others, it is a *cri de cœur* that responds well to counselling. Any number of ingenious methods are used to induce the lesions, from the application of caustics (if these are used inexpertly, signs of trickling of the fluid may be seen) to some form of instrumentation.

Clinical Features

Symptoms

Belle indifférence usually accompanies the eruption.

Morphology

The lesions are bizarre in appearance (Fig. 29.13) and do not conform to the configuration and distribution of any recognized pattern of dermatological disease, even though there may be an attempt to simulate them (Fig. 29.14). Geometrical (Fig. 29.15) and linear-shaped lesions

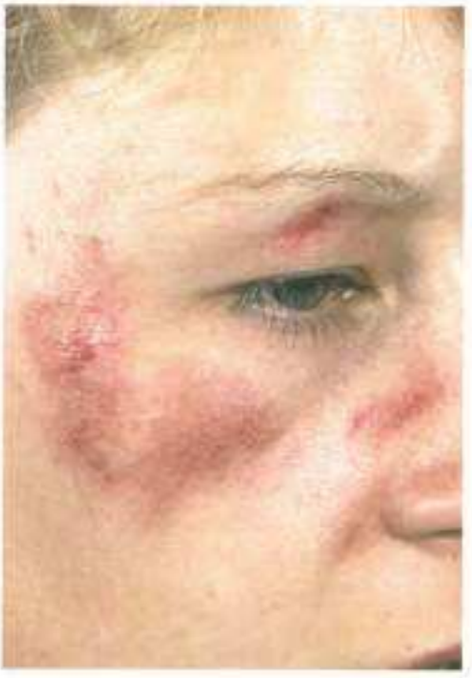


Fig. 29.15 Dermatitis artefacta. It is the linear and bizarre configuration of the disfigurement that will suggest the diagnosis.

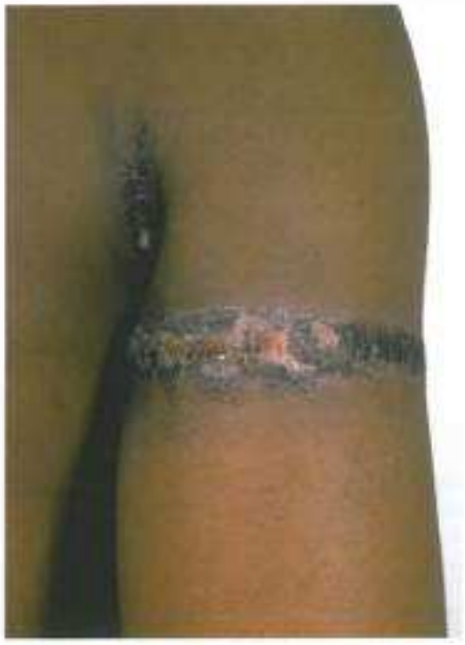


Fig. 29.16 Dermatitis artefacta. The lesions are bizarre in appearance and the cause (in this case a ligature) may sometimes be obvious.

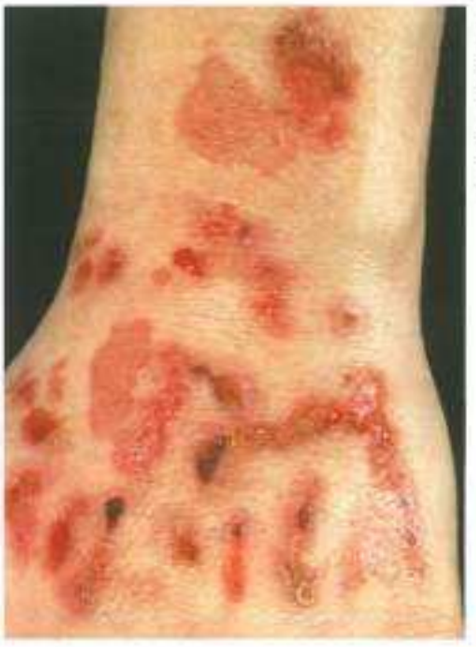


Fig. 29.17 Dermatitis artefacta. Linear excoriations were present on the back of this young woman's hand, with no cutaneous abnormalities elsewhere. The lesions were self-induced.

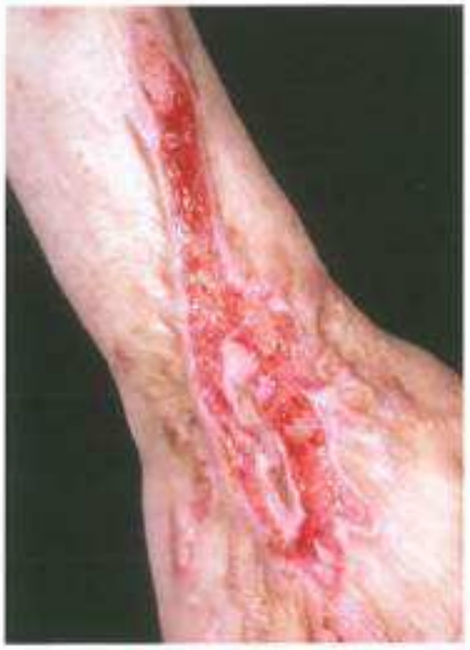


Fig. 29.18 Dermatitis artefacta. This deep, destructive form of interference with the skin and subcutaneous tissues leading to severe mutilation has a poor prognosis.

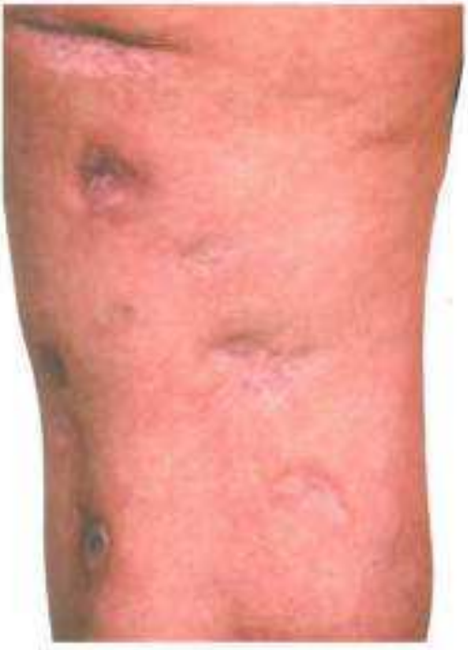


Fig. 29.19 Scarring. A number of methods may be employed to injure the skin and self-harm and have resulted here in various arrangements of scars.

(Figs 29.16 and 29.17) are present. Gross mutilation may occur (Fig. 29.18). Scarring (Fig. 29.19) may occur from any number of factitious injuries to the skin perpetrated by the patient. Extravasation of cytotoxics during intravenous chemotherapy (Fig. 29.20) and scarring from mainlining heroin (Fig. 18.140) is easily distinguished.

Distribution

Exposed sites such as the face and hands.

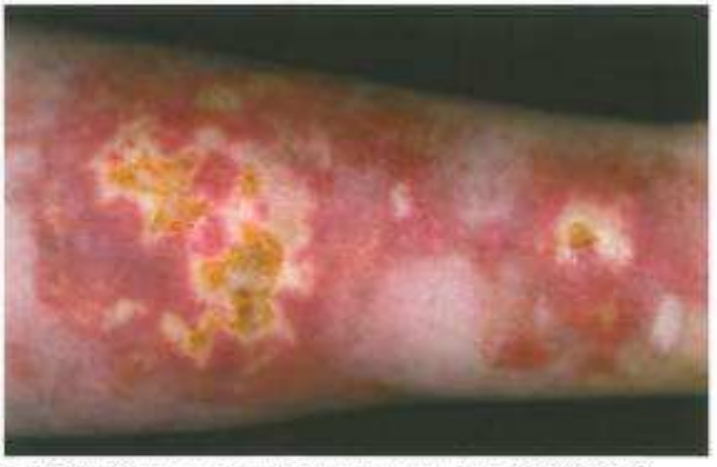


Fig. 29.20 Extravasation during chemotherapy. Pain, inflammation and sometimes ulceration may occur following extravasation of cytotoxics during chemotherapy.

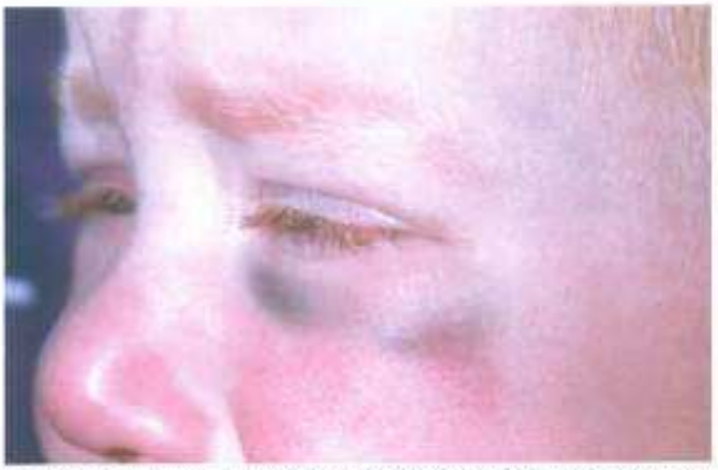


Fig. 29.21 Child abuse. The bruising without adequate or convincing explanation suggests non-accidental injury.

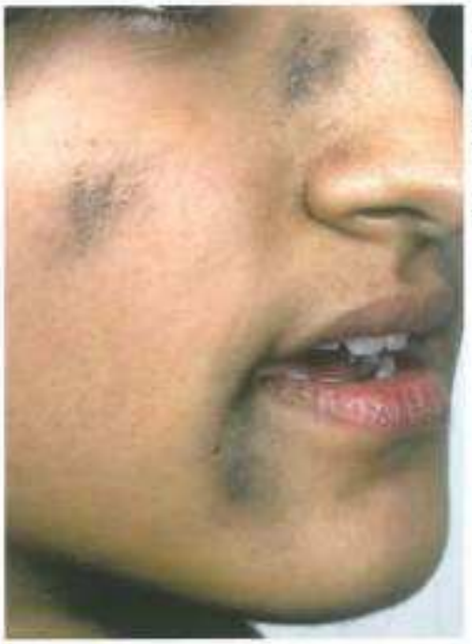


Fig. 29.22 External pigment. This use of external pigments on the skin is a mild form of artefact and indicates unhappiness that can normally be helped successfully and is usually seen in adolescence.

Management

The diagnosis is made because the skin lesions do not conform to the patterns of recognized skin disorders. Non-accidental injury (Fig. 29.21) must, however, be part of the differential diagnosis in childhood. Minor forms (Fig. 28.22) can usually be discussed quite simply and rectified, but with the major variety, confronting the patient with the truth, that the lesion is self-induced, and psychiatric referral are disastrous because patients do not accept this. The condition requires the greatest skill on the part of the physician, with the building up of an understanding so that elucidation of the reasons for the artefact may become possible. The prognosis for recovery is then quite good.

In the majority, however, it is an exceedingly difficult disorder to manage. If the manifestation is on a part of the body that can be occluded, for example with plaster of Paris, the skin will rapidly heal but inevitably breaks down when the patient is able to interfere with it once more. Nevertheless, this manoeuvre will help to confirm the diagnosis. Hospitalization, skilled nursing and psychotropic drugs may all be helpful.

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Note: Page numbers in **bold** refer to figures and tables

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