WEEDON'S
SKIN PATHOLOGY

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FOURTH EDITION

JAMES W. PATTERSON
MD, FACP, FAAD

Professor of Pathology and Dermatology
Director of Dermatopathology
University of Virginia Health System
Charlottesville, VA
USA

CONTRIBUTOR

GREGORY A. HOSLER MD PHD
Dermatopathologist
ProPath Dermatopathology
Dallas, TX
USA

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Executive Content Strategist: Michael Houston
Content Development Specialist: Nani Clansey
Content Coordinator: Humayra Rahman-Khan
Project Manager: Joanna Souch
Design: Miles Hitchen
Marketing Manager(s) (UK/USA): Veronica Short

PREFACE

From the time Dr. Phil Cooper handed me a copy of Volume 9 of *Systemic Pathology: The Skin* by David Weedon, published in 1992, I realized that here indeed was a work of distinction, different from any other I had encountered: exquisitely thorough in detail but also filled with practical diagnostic advice. I eagerly sought the subsequent editions (the second edition quickly became worn out and had to be rebound; the third is well on its way to the same fate), using them in teaching dermatology and pathology residents and dermatopathology fellows. Little did I know that I would one day be preparing the fourth edition. Despite the familiarity with the book one develops through teaching with it and using it in daily practice, one gains a completely different perspective when actually editing and updating such a work. It was through that effort that I came to fully appreciate the significance of Dr. Weedon's monumental achievement in creating *Skin Pathology*, which in its way, in my view, ranks with Osler's *Principles and Practice of Medicine*, first published more than a century ago (1892).

And that's when the pressure *really* begins! One quickly realizes the need to maintain the overall high quality, scientific accuracy, and style that have become so familiar but also to make the kinds of meaningful changes that can keep the book fresh and up-to-date while at the same time not adding so much material that the work is bogged down in detail and becomes impractical. It is my hope that, to some extent, this goal has been achieved.

On first opening this volume, I hope that regular readers will have that comfortable sense of familiarity with the organization and writing style. Despite the advances of the past 4 or 5 years, much of the basic information about cutaneous diseases remains valid, and certainly much of the descriptive histopathology of established disorders remains the same. For the most part, I have also left the opinions on certain dermatopathologic controversies intact (e.g., the issue of 'hypersensitivity dermatitis') because on the majority of these issues we are in full agreement. So the book ought to read pretty much as one would expect 'Weedon' to read!

On the other hand, there are clearly some changes. First and foremost, of course, are updates on cutaneous diseases based on the literature of the past 4 or 5 years. The output of scientific information in this short period of time has been nothing less than extraordinary; for some diseases, there are literally thousands of new references, contributed by clinicians and scientists throughout the globe. A large part of the author's/editor's task is to make a decision as to which studies should be included and which should not. Reviews of recent advances, breakthroughs in the understanding of diseases at the molecular level, and new methods of enhancing diagnostic accuracy obviously receive priority. The bar is set higher for inclusion of case reports, but these, too, are cited when they provide significant insights into a disease or when, for example, they show that a disease occurs in a particular anatomic site more often than expected, or that a previously overlooked histopathologic finding can be of significant diagnostic importance.

Second, I have placed increasing emphasis on differential diagnosis, which was always there, of course, but embedded in the general histopathology discussion. Differential diagnosis has now been promoted to a separate section, with a heading at the same level as 'Histopathology.' The information in these sections has been extracted from other portions of the text, from my own experience, and from recent literature focused on this topic. It is hoped that this will make diagnostically useful information more readily accessible when working at the microscope. Third, it is my belief that every bit of information that can contribute in any way to the diagnostic process ought to be included in this text. Therefore, there are short sections on the features seen on fine needle aspiration cytology, dermoscopy, and confocal laser microscopy; these are usually found, but set apart, in the Histopathology sections. Fourth, I have de-emphasized the sections on therapy. These are still included because an all-important fact is that therapeutic intervention changes the microscopic appearance of cutaneous disease, placing a particular burden on the pathologist when the 'classic' features of a disease are not present! The therapy sections for the most part no longer appear under a separate heading but are included, usually, as the last paragraph in the general discussion of a disease entity. They consist largely of lists of therapeutic agents, without detailed analyses of risks and benefits – it being believed that this information is presented in greater detail in volumes devoted to clinical dermatology and therapeutics. Fifth, a number of new figures have been added – 425 in all, or an average of more than 10 per chapter.

Although the organization of chapters is largely the same as in the previous edition, in two instances significant changes have been made. Many of the sections on melanoma in Chapter 32 (Lentigines, Nevi, and Melanomas) have been extensively rewritten by Dr. Gregory A. Hosler. These include Incidence and Mortality, Risk Factors, Pathogenesis, Classification, Special Techniques to Aid Diagnosis, Prognostic Factors and Survival, and Management. In Chapter 33 (Tumors of Cutaneous Appendages), the grouping of conditions has been changed, and in particular apocrine and eccrine tumors are combined into one section. This is done largely for the convenience of the reader; thus, the poroma group is discussed together, as are the hidradenomas (apocrine and poroid). Current information about the lines of differentiation of these tumors is still provided – but with the realization that the 'final word' vis-à-vis apocrine versus eccrine differentiation probably has yet to be written! Newly reported drugs or other agents producing various dermatoses (e.g., acute generalized exanthematous pustulosis, lichenoid drug eruptions, and pityriasiform eruptions) have been added to sections and tables in the relevant chapters. It is the nature of the subject of drug reactions that much of this information is scattered throughout the text. Thus, the actual chapter on cutaneous drug reactions (Chapter 20) has been focused on a general discussion of drug reactions, a review of major categories of offending drugs, and a consideration of a few unique types of eruptions (e.g., the halogenodermas) while providing page references to the other types of eruptions considered elsewhere in the text. That organization is retained in this edition, in part to avoid needless duplication of information.

I express my gratitude to Dr. Gregory Hosler for his excellent updated sections on melanoma and to Dr. Mark R. Wick for his contribution of several figures, including fluorescent *in situ* hybridization (FISH) images. I also wish to thank Dr. Geoffrey Strutton for his original contributions to the chapters on Vascular Tumors and Cutaneous Infiltrates – Lymphomatous and Leukemic. My deep appreciation goes to Michael Houston, Executive Content Strategist for Elsevier Ltd., and Nani Clansey, Humayra Rahman-Khan, Joanna Souch, Dan Hays, and Susan Stuart for their patience and help in the production of this volume.

To Julie and Wyatt, with love and gratitude for their support,
and to David Weedon, with the utmost admiration and respect.

An approach to the interpretation of skin biopsies

1

INTRODUCTION

Dermatopathology requires years of training and practice to attain an acceptable level of diagnostic skill. Many have found this process an exciting and challenging one, well worth the expenditure of time and intellectual effort. To the trainee, there seems to be an endless number of potential diagnoses in dermatopathology, with many bewildering names. However, if a logical approach is adopted, the great majority of skin biopsies can be diagnosed specifically and the remainder can be partly categorized into a particular group of diseases. This learning process can be enhanced under the tutelage of a skilled mentor and by 'optical mileage', a term used for the self-examination and diagnosis of large amounts of day-to-day material; such cases invariably differ from 'classic' examples of an entity found in teaching sets. It should not be forgotten that the histopathological features of some dermatoses are not diagnostically specific, and it may only be possible in these circumstances to state that the histopathological features are 'consistent with' the clinical diagnosis.

The interpretation of many skin biopsies requires the identification and integration of two different, morphological features – the *tissue reaction pattern* and the *pattern of inflammation*. This is a crude algorithmic approach; more sophisticated ones usually hinder rather than enhance the ability to make a specific diagnosis.

Tissue reaction patterns are distinctive morphological patterns that categorize a group of cutaneous diseases. Within each of these histopathological categories there are diseases that may have similar or diverse clinical appearances and etiologies. Some diseases may show histopathological features of more than one reaction pattern at a particular time or during the course of their evolution. Such cases may be difficult to diagnose. In this edition, an attempt has been made to list diseases that characteristically express more than one tissue reaction pattern (presented later).

The *pattern of inflammation* refers to the distribution of the inflammatory cell infiltrate within the dermis and/or the subcutaneous tissue. There are several distinctive patterns of inflammation (discussed later): their recognition assists in making a specific diagnosis.

Some dermatopathologists base their diagnostic approach on the inflammatory pattern, whereas others look first to see if the biopsy can be categorized into one of the 'tissue reactions' and use the pattern of inflammation to further categorize the biopsy within each of these reaction patterns. In practice, the experienced dermatopathologist sees these two aspects (tissue reaction pattern and inflammatory pattern) simultaneously, integrating and interpreting the findings in a matter of seconds. For trainees in dermatopathology, the use of tissue reaction patterns, combined with the mnemonic for diseases with a superficial and deep inflammatory pattern, appears to be the easiest method to master.

The categorization of inflammatory dermatoses by their tissue reactions is considered first.

Tissue reaction patterns

There are many different reaction patterns in the skin, but the majority of inflammatory dermatoses can be categorized into six different patterns. For convenience, these are called the *major tissue reaction patterns*. Occasionally, diseases express more than one major pattern, either *ab initio* or during their evolution. They are dealt with separately in the 'Combined reaction patterns' section. There are a number of other diagnostic reaction patterns that occur much less commonly than the major group of six but that are nevertheless specific for other groups of dermatoses. These patterns are referred to as *minor tissue reaction patterns*. They are considered after the major reaction patterns.

Patterns of inflammation

There are four patterns of cutaneous inflammation characterized on the basis of distribution of inflammatory cells within the skin:

1. Superficial perivascular inflammation
2. Superficial and deep dermal inflammation
3. Folliculitis and perifolliculitis
4. Panniculitis.

There are numerous dermatoses showing a superficial perivascular inflammatory infiltrate in the dermis and a limited number in the other categories. Sometimes panniculitis and folliculitis are regarded as major tissue reaction patterns because of their easily recognizable pattern.

MAJOR TISSUE REACTION PATTERNS

A significant number of inflammatory dermatoses can be categorized into one of the following six major reaction patterns, the key morphological feature of which is included in parentheses:

1. *Lichenoid* (basal cell damage; interface dermatitis)
2. *Psoriasiform* (regular epidermal hyperplasia)
3. *Spongiotic* (intraepidermal intercellular edema)
4. *Vesiculobullous* (blistering within or beneath the epidermis)
5. *Granulomatous* (chronic granulomatous inflammation)
6. *Vasculopathic* (pathological changes in cutaneous blood vessels).

Each of these reaction patterns is discussed in turn, together with a list of the dermatoses found in each category.

THE LICHENOID REACTION PATTERN ('INTERFACE DERMATITIS')

The lichenoid reaction pattern ('interface dermatitis') (see Chapter 3) is characterized by *epidermal basal cell damage*, which may be manifested by cell death and/or basal vacuolar change (known in the past as 'liquefaction degeneration'). The basal cell death usually presents in the form of shrunken eosinophilic cells, with pyknotic nuclear remnants, scattered along the basal layer of the epidermis (**Fig. 1.1**). These cells are known as Civatte bodies. They are undergoing death by apoptosis, a morphologically distinct type of cell death seen in both physiological and pathological circumstances (see p. 38). Sometimes the basal cell damage is quite subtle, with only an occasional Civatte body and very focal vacuolar change. This is a feature of some drug reactions.

In the United States, the term **'interface dermatitis'** is used synonymously with the lichenoid reaction pattern, although it is not usually applied to the subtle variants. Its use in other countries is by no means universal. At other times, it is used for the morphological subset (discussed later) in which inflammatory cells extend into the basal layer or above. The term is widely used despite its lack of precision. It is warmly embraced as a diagnosis, but it is nothing more than a pattern, encompassing many clinical entities with diverse presentations, etiologies, and treatments.

A distinctive subgroup of the lichenoid reaction pattern is the *poikilodermatous pattern*, characterized by mild basal damage, usually of vacuolar type, associated with epidermal atrophy, pigment incontinence, and dilatation of vessels in the papillary dermis (**Fig. 1.2**). It is a feature of the various types of poikiloderma (see p. 75).

The specific diagnosis of a disease within the lichenoid tissue reaction requires an assessment of several other morphological features, including the following:

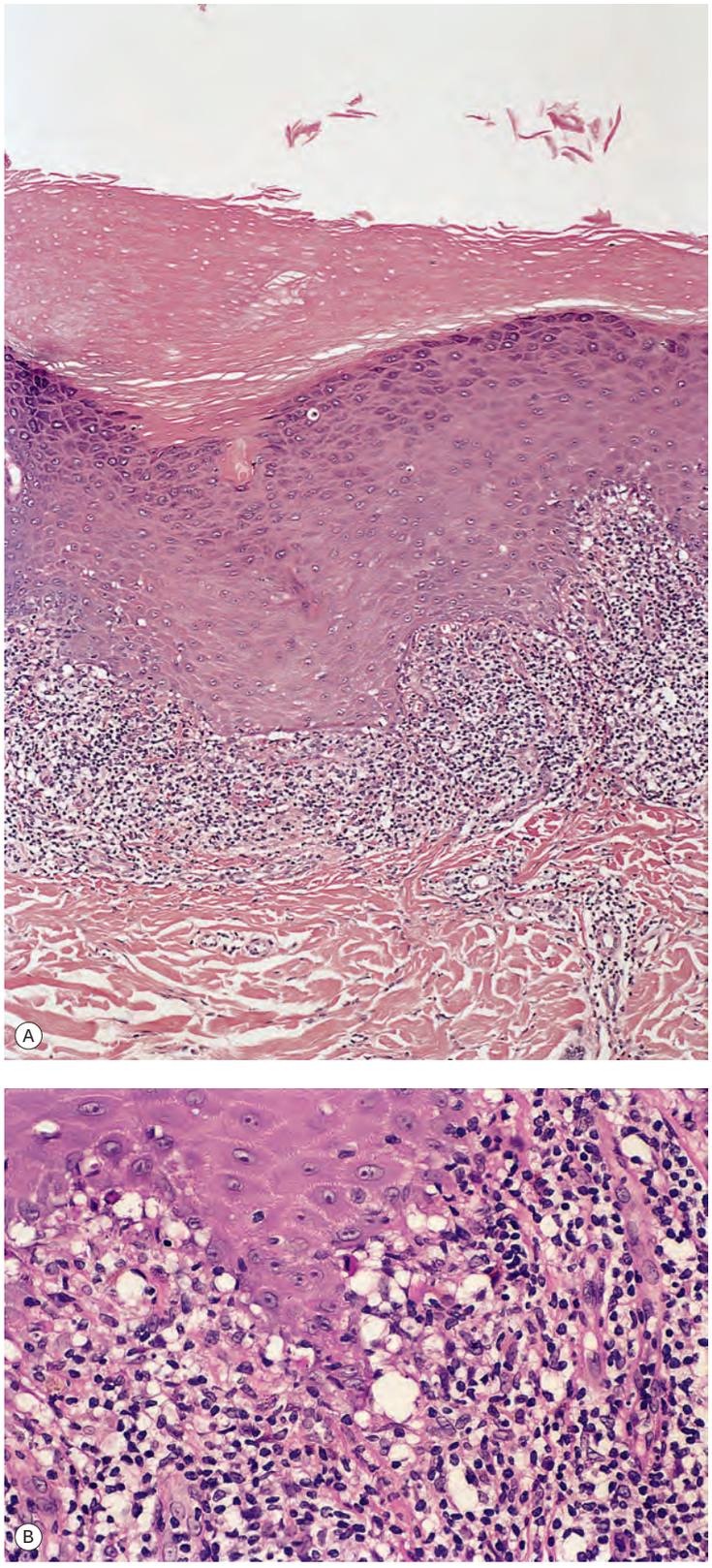

Figure 1.1 The lichenoid reaction pattern. (A) There are shrunken keratinocytes with pyknotic nuclear remnants (Civatte bodies) in the basal layer. These cells are undergoing death by apoptosis. **(B)** There is also focal vacuolar change. (H&E)

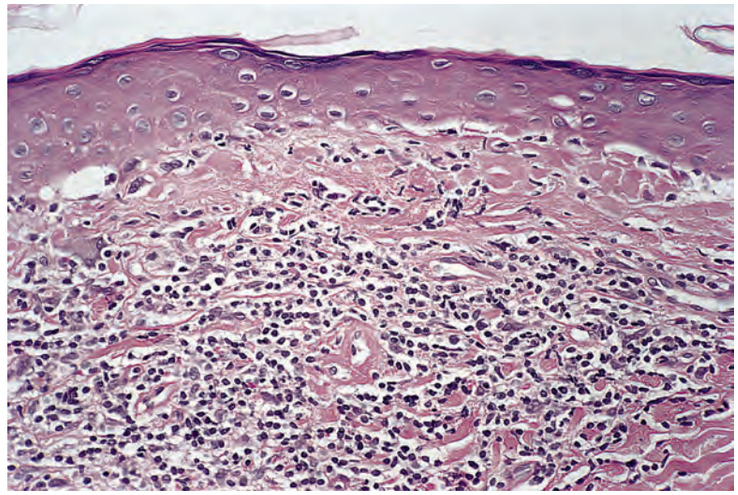

Figure 1.2 The poikilodermatous variant of the lichenoid reaction pattern. It is characterized by mild vacuolar change of the basal layer of the epidermis, mild epidermal atrophy, and dilatation of vessels in the papillary dermis. (H&E)

1. The *type of basal damage* (vacuolar change is sometimes more prominent than cell death in lupus erythematosus, dermatomyositis, the poikilodermas, and drug reactions)
2. The *distribution of the accompanying inflammatory cell infiltrate* (the infiltrate touches the undersurface of the basal layer in lichen planus and its variants, early lichen sclerosus et atrophicus, and in disseminated superficial actinic porokeratosis; it obscures the dermoepidermal interface (so-called 'interface dermatitis') in erythema multiforme, paraneoplastic pemphigus, fixed drug eruptions, acute pityriasis lichenoides (PLEVA), acute graft-versus-host disease (GVHD), one variant of lupus erythematosus, and reactions to phenytoin (Dilantin®) and other drugs; and it involves the deep as well as the superficial part of the dermis in lupus erythematosus, syphilis, photolichenoid eruptions, and some drug reactions)
3. The presence of *prominent pigment incontinence* (as seen in drug reactions, the poikilodermas, lichenoid reactions in dark-skinned people, and some of the sun-exacerbated lichen planus variants, such as lichen planus actinicus)
4. The presence of *satellite cell necrosis* (lymphocyte-associated apoptosis) – defined here as two or more lymphocytes in close proximity to a Civatte body (a feature of graft-versus-host reaction, regressing plane warts, subacute radiation dermatitis, erythema multiforme, and some drug reactions).

The diseases showing the lichenoid reaction pattern are listed in **Table 1.1**.

THE PSORIASIFORM REACTION PATTERN

From a morphological standpoint, the psoriasiform tissue reaction (see Chapter 4) is defined as *epidermal hyperplasia in which there is elongation of the rete ridges, usually in a regular manner* (**Fig. 1.3**).

It is acknowledged that this approach has some shortcomings because many of the diseases in this category, including psoriasis, show no significant epidermal hyperplasia in their early stages. Rather, dilated vessels in the papillary dermis and an overlying suprapapillary scale may be the dominant features in early lesions of psoriasis. Mitoses are increased in basal keratinocytes in this pattern, particularly in active lesions of psoriasis.

The psoriasiform reaction pattern was originally defined as the cyclic formation of a suprapapillary exudate with focal parakeratosis

Table 1.1 Diseases showing the lichenoid reaction pattern ('interface dermatitis')
Lichen planus
Lichen planus variants*
Lichen nitidus
Lichen striatus
Lichen planus-like keratosis
Lichenoid drug eruptions*
Fixed drug eruptions*
Erythema multiforme and variants*
Superantigen 'id' reaction*
Graft-versus-host disease*
Subacute radiation dermatitis*
Eruption of lymphocyte recovery
AIDS interface dermatitis
Lupus erythematosus*
Dermatomyositis
Poikiloderma congenita(le)*
Kindler's syndrome
Congenital telangiectatic erythema (Bloom's syndrome)
Lichen sclerosus et atrophicus
Dyskeratosis congenita
Poikiloderma of Civatte
Pityriasis lichenoides*
Persistent viral reactions
Perniosis
Polymorphic light eruption (pinpoint type)
Paraneoplastic pemphigus
Lichenoid purpura
Lichenoid contact dermatitis
Still's disease (adult onset)
Late secondary syphilis
Porokeratosis
Drug eruptions
Phototoxic dermatitis
Prurigo pigmentosa
Erythroderma
Mycosis fungoides
Regressing warts and tumors
Regressing pityriasis rosea
Lichen amyloidosus
Vitiligo
Lichenoid tattoo reaction
Diseases marked with an * may have a true interface pattern.

related to it. The concept of the 'squirting dermal papilla' was also put forward with the suggestion that serum and inflammatory cells escaped from the blood vessels in the papillary dermis and passed through the epidermis to form the suprapapillary exudate referred to previously. This 'concept', although outmoded, is useful in considering early lesions of psoriasis in which dilated vessels and surface suprapapillary scale are often the only features. The epidermal hyperplasia that also occurs was regarded as a phenomenon secondary to these other processes.

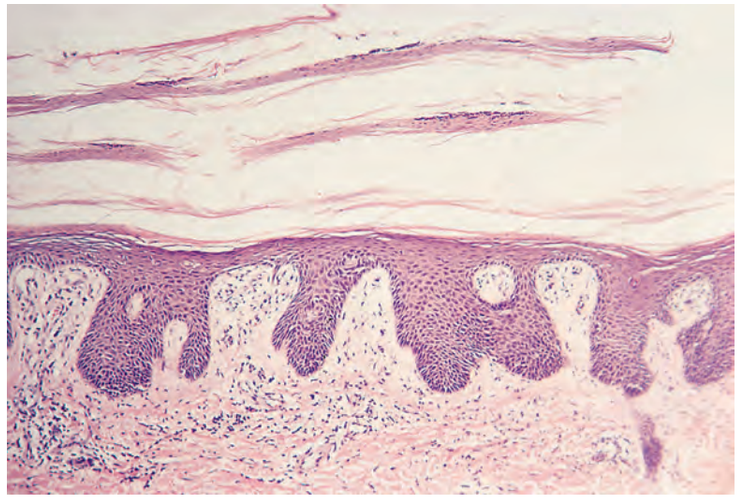

Figure 1.3 The psoriasiform reaction pattern showing epidermal hyperplasia with regular elongation of the rete processes. There are several layers of scale resulting from intermittent 'activity' of the process. (H&E)

Table 1.2 Diseases showing the psoriasiform reaction pattern
Psoriasis
Psoriasiform keratosis
AIDS-associated psoriasiform dermatitis
Pustular psoriasis
Reiter's syndrome
Pityriasis rubra pilaris
Parapsoriasis
Lichen simplex chronicus
Benign alveolar ridge keratosis
Subacute and chronic spongiotic dermatitides
Erythroderma
Mycosis fungoides
Chronic candidosis and dermatophytoses
Inflammatory linear verrucous epidermal nevus (ILVEN)
Norwegian scabies
Bowen's disease (psoriasiform variant)
Clear cell acanthoma
Lamellar ichthyosis
Pityriasis rosea ('herald patch')
Pellagra
Acrodermatitis enteropathica
Glucagonoma syndrome
Secondary syphilis

Diseases showing the psoriasiform reaction pattern are listed in **Table 1.2**.

THE SPONGIOTIC REACTION PATTERN

The spongiotic reaction pattern (see Chapter 5) is characterized by *intraepidermal intercellular edema (spongiosis)*. It is recognized by the

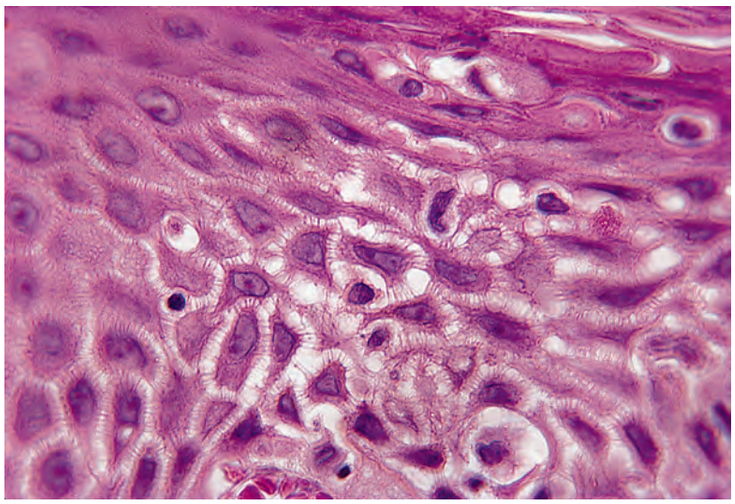

Figure 1.4 The spongiotic reaction pattern. There is mild intercellular edema with elongation of the intercellular bridges. (H&E)

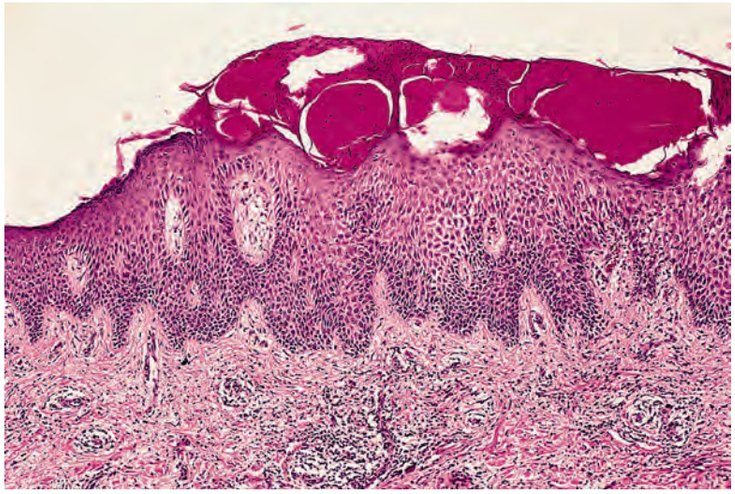

Figure 1.5 The spongiotic reaction pattern in a lesion of some duration. Psoriasiform hyperplasia coexists with the spongiosis. (H&E)

presence of widened intercellular spaces between keratinocytes, with elongation of the intercellular bridges (**Fig. 1.4**). The spongiosis may vary from microscopic foci to grossly visible vesicles. This reaction pattern has been known in the past as the 'eczematous tissue reaction'. Inflammatory cells are present within the dermis, and their distribution and type may aid in making a specific diagnosis within this group. This is the most difficult reaction pattern in which to make a specific clinicopathological diagnosis; often a diagnosis of 'spongiotic reaction consistent with …' is all that can be made.

The major diseases within this tissue reaction pattern (atopic dermatitis, allergic and irritant contact dermatitis, nummular dermatitis, and seborrheic dermatitis) all show progressive psoriasiform hyperplasia of the epidermis with chronicity (**Fig. 1.5**). This change is usually accompanied by diminishing spongiosis, but this will depend on the activity of the disease. Both patterns may be present in the same biopsy. The psoriasiform hyperplasia is, in part, a response to chronic rubbing and scratching.

Six patterns of spongiosis can be recognized:

1. *Neutrophilic spongiosis* (where there are neutrophils within foci of spongiosis)

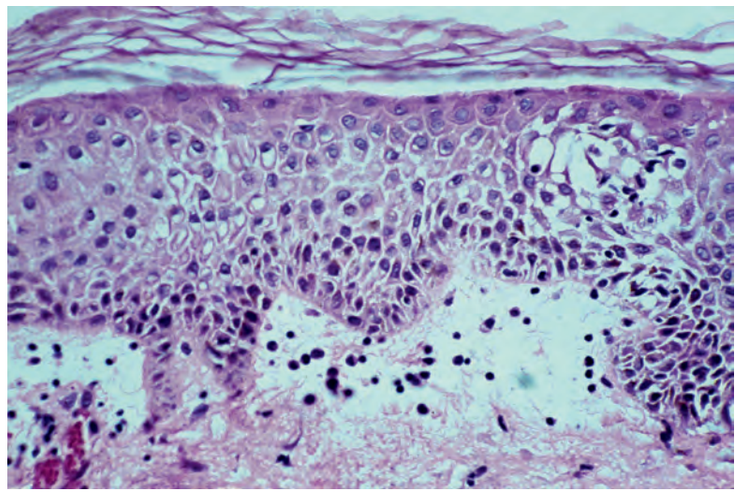

Figure 1.6 Epidermal spongiosis combined with subepidermal edema. This combination characterizes a certain group of diseases. (H&E)

2. *Eosinophilic spongiosis* (where there are numerous eosinophils within foci of spongiosis)
3. *Miliarial (acrosyringial) spongiosis* (where the edema is related to the acrosyringium)
4. *Follicular spongiosis* (where the spongiosis is centered on the follicular infundibulum)
5. *Pityriasiform spongiosis* (where the spongiosis forms small vesicles containing lymphocytes, histiocytes, and Langerhans cells)
6. *Haphazard spongiosis* (the other spongiotic disorders in which there is no particular pattern of spongiosis).

The diseases showing the spongiotic reaction pattern are listed in **Table 1.3(a)**.

A seventh pattern, which is really a variant of haphazard spongiosis, combines epidermal spongiosis with subepidermal edema (**Fig. 1.6**), which can vary from mild to severe, even forming subepidermal blisters. Its causes are listed in **Table 1.3(b)**.

THE VESICULOBULLOUS REACTION PATTERN

In the vesiculobullous reaction pattern, there are *vesicles or bullae at any level within the epidermis or at the dermoepidermal junction* (see Chapter 6). A specific diagnosis can usually be made in a particular case by assessing three features – the anatomical level of the split, the underlying mechanism responsible for the split, and, in the case of subepidermal lesions, the nature of the inflammatory infiltrate in the dermis.

The *anatomical level of the split* may be subcorneal, within the stratum malpighii, suprabasal or subepidermal. The *mechanism responsible* for vesiculation may be exaggerated spongiosis, intracellular edema and ballooning (as occurs in viral infections such as herpes simplex), or acantholysis. Acantholysis is the loss of coherence between epidermal cells. It may be a primary phenomenon or secondary to inflammation, ballooning degeneration (as in viral infections of the skin), or epithelial dysplasia. In the case of subepidermal blisters, electron microscopy and immunoelectron microscopy could be used to make a specific diagnosis in most cases. In practice, the subepidermal blisters are subdivided on the basis of the *inflammatory cell infiltrate within the dermis* (**Fig. 1.7**). Knowledge of the immunofluorescence findings is often helpful in categorizing the subepidermal blistering diseases.

Table 1.4 lists the various vesiculobullous diseases, based on the anatomical level of the split and, in the case of subepidermal lesions, the predominant inflammatory cell within the dermis.

Table 1.3(a) Diseases showing the spongiotic reaction pattern

Neutrophilic spongiosis	Nummular dermatitis
Pustular psoriasis/Reiter's syndrome	Lichen striatus (uncommonly)
Prurigo pigmentosa	Gianotti–Crosti syndrome (sometimes)
IgA pemphigus	**Other spongiotic disorders**
Infantile acropustulosis	Irritant contact dermatitis
Acute generalized exanthematous pustulosis	Allergic contact dermatitis
Palmoplantar pustulosis	Nummular dermatitis
Staphylococcal toxic shock syndrome	Sulzberger–Garbe syndrome
Neisserial infections	Seborrheic dermatitis
Dermatophytosis/candidosis	Atopic dermatitis
Beetle (*Paederus*) dermatitis	Papular dermatitis
Pustular contact dermatitis	Pompholyx
Glucagonoma syndrome	Unclassified eczema
Amicrobial pustuloses	Hyperkeratotic dermatitis of the hands
Periodic fever syndromes	Juvenile plantar dermatosis
Eosinophilic spongiosis	Vein graft donor-site dermatitis
Pemphigus (precursor lesions)	Stasis dermatitis
Herpetiform pemphigus	Autoeczematization ('id' reaction)
Pemphigus vegetans	Dermal hypersensitivity reaction/urticarial dermatitis
Bullous pemphigoid/cicatricial pemphigoid	Pityriasis rosea
Herpes gestationis	Papular acrodermatitis of childhood
Idiopathic eosinophilic spongiosis	Spongiotic drug reactions
Eosinophilic, polymorphic, and pruritic eruption	Autoimmune progesterone dermatitis
Allergic contact dermatitis	Estrogen dermatitis
Protein contact dermatitis	Chronic superficial dermatitis
Atopic dermatitis	Perioral dermatitis
Arthropod bites	Blaschko dermatitis
Eosinophilic folliculitis	Psoriasis (spongiotic and site variants)
Incontinentia pigmenti (first stage)	Light reactions (particularly polymorphic light eruption)
Drug reactions	Dermatophytoses
'Id' reaction	Arthropod bites
Still's disease	Grover's disease (spongiotic variant)
Wells' syndrome	Toxic shock syndrome
Miliarial spongiosis	PUPPP
Miliaria (may look pityriasiform on random section)	Herpes gestationis (early)
Follicular spongiosis	Erythema annulare centrifugum (not always pityriasiform)
Infundibulofolliculitis	Figurate erythemas
Atopic dermatitis (follicular lesions)	Pigmented purpuric dermatoses
Apocrine miliaria	Pityriasis alba
Eosinophilic folliculitis	Eczematoid GVHD
Follicular mucinosis	Allograft rejection
Infectious folliculitides	Eruption of lymphocyte recovery
Perioral dermatitis	Lichen striatus
Pityriasiform spongiosis	Lichen simplex chronicus
Pityriasis rosea	Sweet's syndrome
Pityriasiform drug reaction	Erythroderma
Erythema annulare centrifugum	Mycosis fungoides
Allergic contact dermatitis	Acrokeratosis paraneoplastica

Table 1.3(b) Diseases showing spongiosis and subepidermal edema
Arthropod bites and bite-like reactions in lymphoma
Cercarial dermatitis/larva migrans
PUPPP
Autoeczematization
Superantigen 'id' reaction
Allergic contact dermatitis ('dermal type')
Contact urticaria, papular urticaria
Dermal hypersensitivity/urticarial dermatitis
Erysipelas, erysipeloid
Dermatophytoses
Prebullous pemphigoid
Sweet's syndrome
Wells' syndrome
Miliaria rubra
Pompholyx
Polymorphic light eruption
Spongiotic drug reactions (including estrogen/progesterone dermatitis)

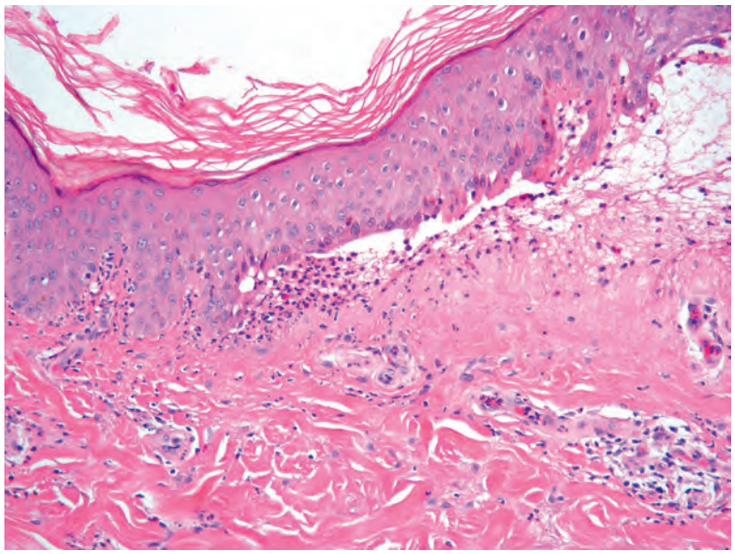

Figure 1.7 The vesiculobullous reaction pattern. In this case, the blister is subepidermal, so further characterization of it requires an assessment of the inflammatory cell infiltrate within the dermis – in this case, neutrophils. (H&E)

THE GRANULOMATOUS REACTION PATTERN

This group of diseases (see Chapter 7) is characterized by the presence of *chronic granulomatous inflammation* – that is, localized collections of epithelioid cells usually admixed with giant cells, lymphocytes, plasma cells, fibroblasts, and nonepithelioid macrophages (Fig. 1.8). Five histological types of granuloma can be identified on the basis of the constituent cells and other changes within the granulomas: sarcoidal, tuberculoid, necrobiotic (collagenolytic), suppurative, and foreign body. A miscellaneous category is usually added to any classification.

Clinically, granulomas present like most other dermal infiltrates, with a mass that is usually firm and is detectable below the skin surface (epidermis) and usually moveable over the deeper tissues. As such, the clinical differential diagnoses include cutaneous tumors and lymphocytic infiltrates.

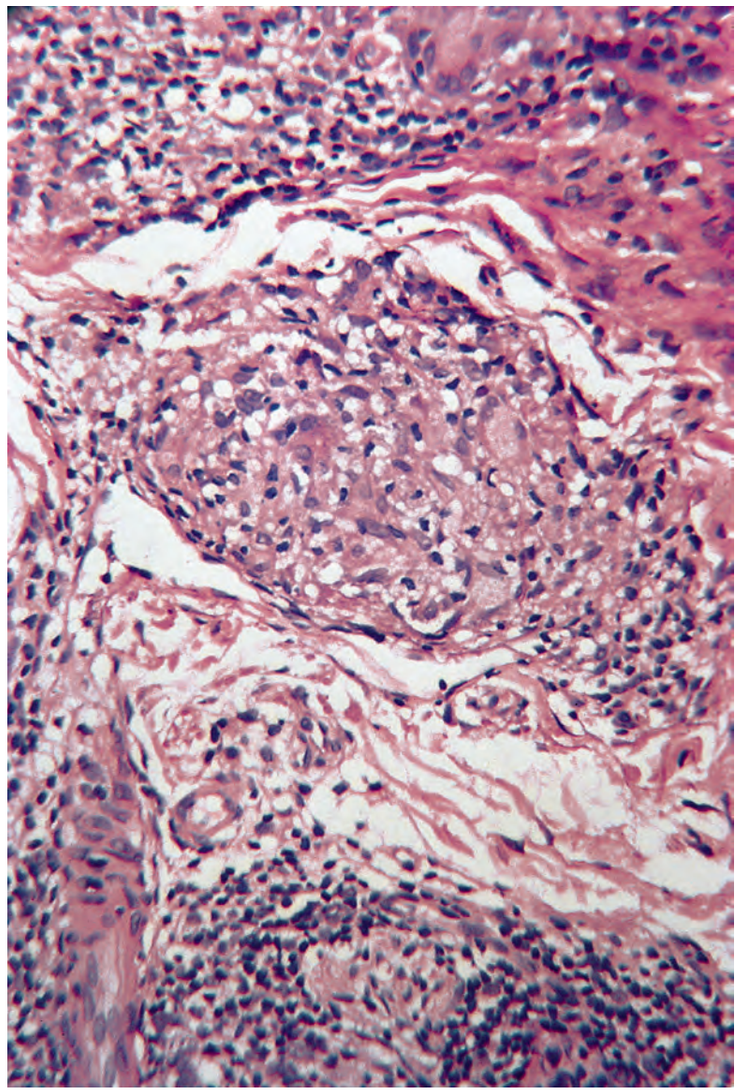

Figure 1.8 The granulomatous reaction pattern. A small tuberculoid granuloma is present in the dermis. (H&E)

Sarcoidal granulomas are composed of epithelioid cells and giant cells, some containing asteroid bodies or other inclusions. The granulomas are often referred to as 'naked granulomas', in that they have only a sparse 'clothing' of peripheral lymphocytes and plasma cells, in contrast to tuberculoid granulomas that usually have more abundant lymphocytes. Some overlap occurs between sarcoidal and tuberculoid granulomas.

Tuberculoid granulomas resemble those seen in tuberculosis, although caseation necrosis is not always present. The giant cells that are present within the granuloma are usually of Langhans type.

Necrobiotic (collagenolytic) granulomas are composed of epithelioid cells, lymphocytes, and occasional giant cells associated with areas of 'necrobiosis' of collagen. Sometimes the inflammatory cells are arranged in a palisade around the areas of necrobiosis. The term 'necrobiosis' has been criticized because it implies that the collagen (which is not a vital structure) is 'necrotic'. Accordingly, the term 'collagenolytic' is now preferred. The process of collagenolysis is characterized by an accumulation of acid mucopolysaccharides between the collagen bundles and degeneration of some interstitial fibroblasts and histiocytes.

Table 1.4 Vesiculobullous diseases

Intracorneal and subcorneal blisters	**Subepidermal blisters with lymphocytes**
Peeling skin syndrome	Erythema multiforme
Adult Still's disease	Paraneoplastic pemphigus
Impetigo	Bullous fixed drug eruption
Staphylococcal 'scalded skin' syndrome	Lichen sclerosus et atrophicus
Dermatophytosis	Lichen planus pemphigoides
Pemphigus foliaceus and erythematosus	Polymorphic light eruption
Herpetiform pemphigus	Fungal infections
Subcorneal pustular dermatosis	Dermal allergic contact dermatitis
IgA pemphigus	Bullous leprosy
Infantile pustular dermatoses	Bullous mycosis fungoides
Acute generalized exanthematous pustulosis	**Subepidermal blisters with eosinophils***
Miliaria crystallina	Wells' syndrome
Intraepidermal (stratum malpighii) blisters	Bullous pemphigoid
Spongiotic blistering diseases	Pemphigoid gestationis
Palmoplantar pustulosis	Arthropod bites (in sensitized individuals)
Amicrobial pustulosis of autoimmune diseases	Drug reactions
Erosive pustular dermatosis of leg	Epidermolysis bullosa
Viral blistering diseases	**Subepidermal blisters with neutrophils***
Epidermolysis bullosa simplex (localized type)	Dermatitis herpetiformis
Friction blister	Linear IgA bullous dermatosis
Suprabasilar blisters	Mucous membrane pemphigoid
Pemphigus vulgaris and vegetans	Ocular cicatricial pemphigoid
Paraneoplastic pemphigus	Localized cicatricial pemphigoid
Hailey–Hailey disease	Deep lamina lucida (anti-p105) pemphigoid
Darier's disease	Anti-p200 pemphigoid
Grover's disease	Bullous urticaria
Acantholytic solar keratosis	Bullous acute vasculitis
Subepidermal blisters with little inflammation	Bullous lupus erythematosus
Epidermolysis bullosa	Erysipelas
Porphyria cutanea tarda and pseudoporphyria	Sweet's syndrome
Bullous pemphigoid (cell-poor variant)	Epidermolysis bullosa acquisita
Burns and cryotherapy	**Subepidermal blisters with mast cells**
Toxic epidermal necrolysis	Bullous urticaria pigmentosa
Suction blisters	**Miscellaneous blistering diseases**
Blisters overlying scars	Drug overdose-related bullae
Bullous solar elastosis	Methyl bromide-induced bullae
Bullous amyloidosis	Etretinate-induced bullae
Waldenström's macroglobulinemia	PUVA-induced bullae
Drug reactions	Cancer-related bullae
Kindler's syndrome	Lymphatic bullae
	Bullous eruption of diabetes mellitus

*Varying admixtures of eosinophils and neutrophils may be seen in cicatricial pemphigoid and late lesions of dermatitis herpetiformis.

Suppurative granulomas have neutrophils within and sometimes surrounding the granuloma. The granulomatous component is not always well formed.

Foreign body granulomas have multinucleate, foreign body giant cells as a constituent of the granuloma. Foreign material can usually be visualized in sections stained with hematoxylin and eosin (H&E), although at other times it requires the use of polarized light for its detection.

The identification of organisms by the use of special stains (the periodic acid–Schiff (PAS) and other stains for fungi and stains for acid-fast bacilli) or by culture may be necessary to make a specific diagnosis. Organisms are usually scanty in granulomas associated with

Table 1.5 Diseases causing the granulomatous reaction pattern

Sarcoidal granulomas	**Suppurative granulomas**
Sarcoidosis	Chromomycosis and phaeohyphomycosis
Blau's syndrome	Sporotrichosis
Reactions to foreign materials	Nontuberculous mycobacterial infection
Secondary syphilis	Blastomycosis
Sézary syndrome	Paracoccidioidomycosis
Herpes zoster scars	Coccidioidomycosis
Systemic lymphomas	Blastomycosis-like pyoderma
Common variable immunodeficiency	Mycetoma, nocardiosis and actinomycosis
Tuberculoid granulomas	Cat-scratch disease
Tuberculosis	Lymphogranuloma venereum
Tuberculids	Pyoderma gangrenosum
Leprosy	Ruptured cysts and follicles
Fatal bacterial granuloma	**Foreign body granulomas**
Late syphilis	Exogenous material
Leishmaniasis	Endogenous material
Protothecosis	**Xanthogranulomas**
Rosacea	**Miscellaneous granulomas**
Idiopathic facial aseptic granuloma	Melkersson–Rosenthal syndrome
Perioral dermatitis	Cutaneous histiocytic lymphangitis
Lupus miliaris disseminatus faciei	Elastolytic granulomas
Crohn's disease	Annular granulomas in ochronosis
Necrobiotic (collagenolytic) granulomas	Granulomas in immunodeficiency disorders
Granuloma annulare	Neutrophilic granulomatous dermatitis
Necrobiosis lipoidica	Interstitial granulomatous dermatitis
Necrobiotic xanthogranuloma	Interstitial granulomatous drug reaction
Rheumatoid nodules	Superantigen 'id' reaction
Rheumatic fever nodules	Granulomatous T-cell lymphomas
Reactions to foreign materials and vaccines	
Crohn's disease	

infectious diseases. The distribution of the granulomas (they may be arranged along nerve fibers in tuberculoid leprosy) may assist in making a specific diagnosis.

Note that many of the infectious diseases listed in **Table 1.5** as causing the granulomatous tissue reaction can also produce inflammatory reactions that do not include granulomas, depending on the stage of the disease and the immune status of the individual.

THE VASCULOPATHIC REACTION PATTERN

The vasculopathic reaction pattern (see Chapter 8) includes a clinically heterogeneous group of diseases that have in common *pathological changes in blood vessels*. The most important category within this tissue reaction pattern is *vasculitis*, which can be defined as an inflammatory process involving the walls of blood vessels of any size (**Fig. 1.9**). Some dermatopathologists insist on the presence of fibrin within the vessel wall before they will accept a diagnosis of vasculitis. This criterion is far too restrictive, and it ignores the fact that exudative features, such as fibrin extravasation, are not prominent in chronic inflammation in any tissue of the body. On the other hand, a diagnosis of vasculitis should not be made simply because there is a perivascular infiltrate of inflammatory cells. Notwithstanding these comments, in resolving and late lesions of vasculitis there may only be a tight perivascular inflammatory cell infiltrate, making it difficult to make a diagnosis of vasculitis. Some of these cases may represent a cell-mediated attack on vessel walls. Endothelial cells, like epidermal Langerhans cells, are antigen processing cells and could evoke an inflammatory response. The presence of endothelial swelling in small vessels and an increase in fibrohistiocytic cells (a 'busy dermis') and sometimes acid mucopolysaccharides in the dermis are further clues that assist in confirming that a resolving vasculitis is present. Although it is useful to categorize vasculitis into acute, chronic lymphocytic, and granulomatous forms, it should be remembered that an acute vasculitis may progress with time to a chronic stage. Fibrin is rarely present in these late lesions.

Other categories of vascular disease include non-inflammatory purpuras, vascular occlusive diseases, and urticarias. The purpuras are characterized by extravasation of erythrocytes and the vascular occlusive diseases by fibrin and/or platelet thrombi or, rarely, other material in the lumen of small blood vessels. The urticarias are characterized by increased vascular permeability, with escape of edema fluid and some cells into the dermis. The neutrophilic dermatoses are included also because they share some morphological features with the acute vasculitides.

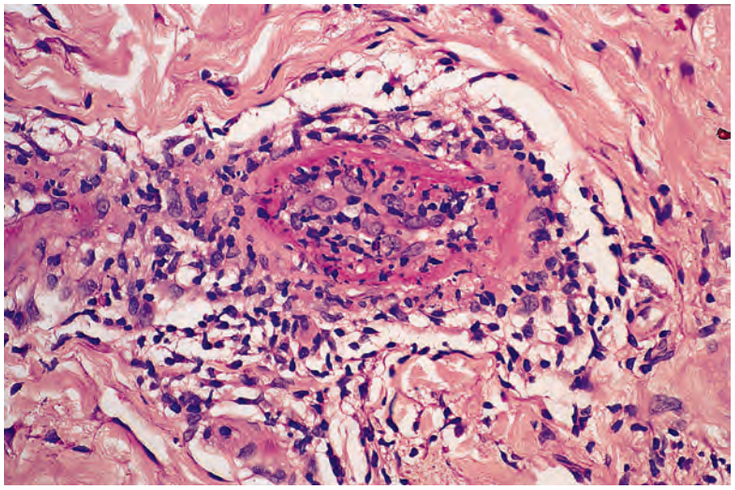

Figure 1.9 Acute vasculitis. Neutrophils are present in the wall of a vessel that also shows extravasation of fibrin. (H&E)

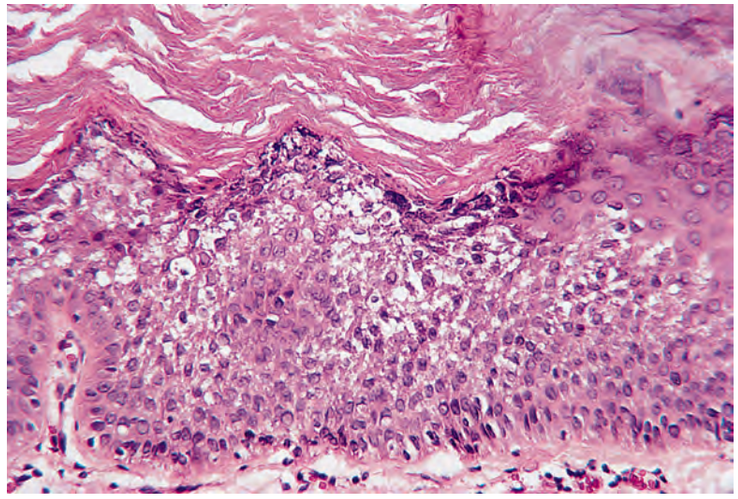

Figure 1.10 Epidermolytic hyperkeratosis characterized by granular and vacuolar degeneration of the upper layers of the epidermis and overlying hyperkeratosis. (H&E)

The diseases showing the vasculopathic reaction pattern are listed in **Table 1.6**.

COMBINED REACTION PATTERNS

As mentioned previously, sometimes more than one of the major tissue reaction patterns is present in a particular disease, either as a feature of the evolution of the disease or as a characteristic feature of all stages of that condition. The combination of spongiotic and psoriasiform patterns is part of the evolution of many spongiotic diseases; it is not considered further.

The combinations most frequently encountered include lichenoid and spongiotic, lichenoid and granulomatous, and lichenoid and vasculopathic.

The various diseases that show these dual patterns are listed in **Table 1.7**.

MINOR TISSUE REACTION PATTERNS

'Minor tissue reaction patterns' is a term of convenience for a group of reaction patterns in the skin that are seen much less frequently than the six major patterns already discussed. Like the major reaction patterns, each of the patterns to be considered here is diagnostic of a certain group of diseases of the skin. Sometimes, a knowledge of the clinical distribution of the lesions (e.g., whether they are localized, linear, zosteriform, or generalized) is required before a specific clinicopathological diagnosis can be made. The minor tissue reaction patterns to be discussed, with their key morphological feature in parentheses, are as follows:

1. *Epidermolytic hyperkeratosis* (hyperkeratosis with granular and vacuolar degeneration)
2. *Acantholytic dyskeratosis* (suprabasilar clefts with acantholytic and dyskeratotic cells)
3. *Cornoid lamellation* (a column of parakeratotic cells with absence of an underlying granular layer)
4. *Papillomatosis* – 'church-spiring' (undulations and protrusions of the epidermis)
5. *Angiofibromas* (increased dermal vessels with surrounding fibrosis)
6. *Eosinophilic cellulitis with 'flame figures'* (dermal eosinophils and eosinophilic material adherent to collagen bundles)
7. *Transepithelial elimination* (elimination of material via the epidermis or hair follicles).

The first four patterns listed are all disorders of epidermal maturation and keratinization. They are discussed briefly here and in further detail in Chapter 9. Angiofibromas are included with tumors of fibrous tissue in Chapter 34, whereas eosinophilic cellulitis is discussed with the cutaneous infiltrates in Chapter 40. Transepithelial elimination is a process that may occur as a secondary event in a wide range of skin diseases. It is discussed later.

EPIDERMOLYTIC HYPERKERATOSIS

The features of the epidermolytic hyperkeratotic reaction pattern are *compact hyperkeratosis accompanied by granular and vacuolar degeneration of the cells of the spinous and granular layers* (**Fig. 1.10**). This pattern may occur in diseases or lesions that are generalized (bullous ichthyosiform erythroderma), systematized (epidermal nevus variant), palmar–plantar (a variant of palmoplantar keratoderma), solitary (epidermolytic acanthoma), multiple and discrete (disseminated epidermolytic acanthoma), or follicular (nevoid follicular hyperkeratosis). Rarely, this pattern may be seen in solar keratoses. Not uncommonly, epidermolytic hyperkeratosis is an incidental finding in a biopsy taken because of the presence of some other lesion.

ACANTHOLYTIC DYSKERATOSIS

Acantholytic dyskeratosis is characterized by *suprabasilar clefting with acantholytic and dyskeratotic cells at all levels of the epidermis* (see p. 302) (**Fig. 1.11**). It may be a generalized process (Darier's disease), a systematized process (a variant of epidermal nevus), transient (Grover's disease), palmar–plantar (a very rare form of keratoderma), solitary (warty dyskeratoma), an incidental finding, or a feature of a solar keratosis (acantholytic solar keratosis).

CORNOID LAMELLATION

Cornoid lamellation (**Fig. 1.12**) is localized faulty keratinization characterized by a thin column of parakeratotic cells with an absent or decreased underlying granular zone and vacuolated or dyskeratotic cells in the spinous layer (see p. 299). Although cornoid lamellation is

Table 1.6 Diseases showing the vasculopathic reaction pattern

Non-inflammatory purpuras	Sweet's syndrome
Traumatic purpura	Pustular vasculitis of the hands
Psychogenic purpura	Neutrophilic fixed drug eruption
Drug purpura	Bowel-associated dermatosis–arthritis syndrome
Bleeding diatheses	Rheumatoid neutrophilic dermatosis
Senile purpura	Acute generalized pustulosis
Vascular occlusive diseases	Behçet's disease
Protein C and protein S deficiencies	Abscess-forming neutrophilic dermatosis
Prothrombin gene mutations	**Chronic lymphocytic vasculitis**
Warfarin necrosis	Inherited lymphocytic vasculitis
Atrophie blanche (livedoid vasculopathy)	Toxic erythema
Disseminated intravascular coagulation	Collagen vascular disease
Purpura fulminans	PUPPP
Thrombotic thrombocytopenic purpura	Prurigo of pregnancy
Thrombocythemia	Gyrate and annular erythemas
Cryoglobulinemia	Pityriasis lichenoides
Cholesterol and other types of embolism	Pigmented purpuric dermatoses
Antiphospholipid syndrome	Malignant atrophic papulosis (Degos)
Factor V Leiden mutation	Perniosis
Sneddon's syndrome	Rickettsial and viral infections
CADASIL	Pyoderma gangrenosum
Miscellaneous conditions	Polymorphic light eruption (variant)
Urticarias	TRAPS
Acute vasculitis	Leukemic vasculitis
Leukocytoclastic (hypersensitivity) vasculitis	**Vasculitis with granulomatosis**
Henoch–Schönlein purpura	Crohn's disease
Eosinophilic vasculitis	Drug reactions
Rheumatoid vasculitis	Herpes zoster
Urticarial vasculitis	Infectious granulomatous diseases
Mixed cryoglobulinemia	Wegener's granulomatosis
Hypergammaglobulinemic purpura	Lymphomatoid granulomatosis (angiocentric lymphoma)
Hyperimmunoglobulinemia D syndrome	Churg–Strauss syndrome
Septic vasculitis	Lethal midline granuloma
Erythema elevatum diutinum	Giant cell (temporal) arteritis
Granuloma faciale	Takayasu's arteritis
Localized chronic fibrosing vasculitis	**Miscellaneous vascular disorders**
Microscopic polyangiitis (polyarteritis)	Vascular steal syndrome
Polyarteritis nodosa	Capillary leak syndrome
Kawasaki disease	Vascular calcification
Superficial thrombophlebitis	Pericapillary fibrin cuffs
Sclerosing lymphangitis of the penis	Vascular aneurysms
Miscellaneous associations	Erythermalgia
Neutrophilic dermatoses	Cutaneous necrosis and ulceration
Periodic fever syndromes	Paraneoplastic acral vascular syndrome
Amicrobial pustulosis of the folds	

Table 1.7 Diseases showing combined reaction patterns

Lichenoid and spongiotic
Lichen striatus
Spongiotic drug reactions
Morbilliform drug reactions (may also be vasculopathic)
Lichenoid contact dermatitis
Late-stage pityriasis rosea
Sulzberger–Garbe syndrome (oid-oid disease)
Nummular dermatitis
Superantigen 'id' reactions
DiGeorge syndrome
Gianotti–Crosti syndrome (may also be vasculopathic)
Eczematous GVHD
Lichenoid and granulomatous
Lichenoid sarcoidosis
Lichen nitidus
Lichen striatus (rare)
Secondary syphilis
Herpes zoster (late)
Tinea capitis
Mycobacterial infections
HIV infection
Drug reactions (often in setting of rheumatoid arthritis or Crohn's disease – ACE inhibitors, antihistamines, atenolol, oxacillin, allopurinol, captopril, cimetidine, enalapril, erythropoietin, hydroxychloroquine, simvastatin, diclofenac, quinine, tetracycline, sulfa drugs)
Endocrinopathies
Hepatobiliary disease
Rheumatoid arthritis
Lichenoid and vasculopathic
Pityriasis lichenoides
Perniosis
Polymorphic light eruption (some cases)
Pigmented purpuric dermatoses (PPD)
Persistent viral reactions, particularly to herpes virus
Granulomatous and vasculopathic
Drug reactions (allopurinol, see lichenoid and granulomatous listings above)
Crohn's disease
Granulomatous PPD
Granulomatous vasculitides
Spongiotic and vasculopathic
Rare reactions to viruses
Rare drug reactions

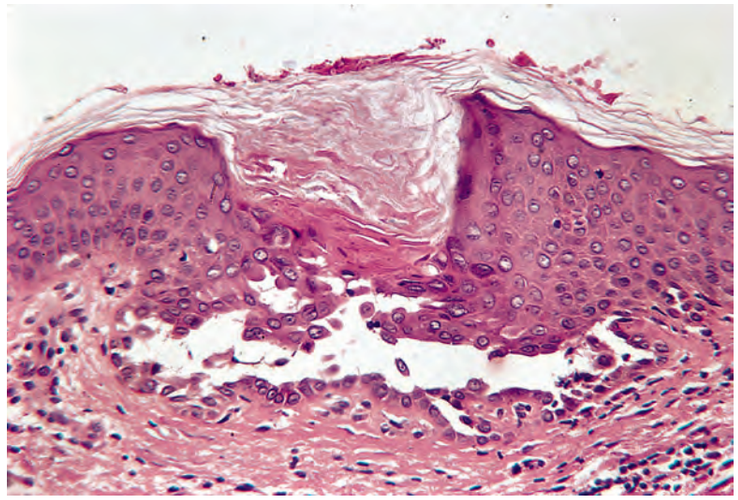

Figure 1.11 Acantholytic dyskeratosis with suprabasal clefting and dyskeratotic cells in the overlying epidermis. (H&E)

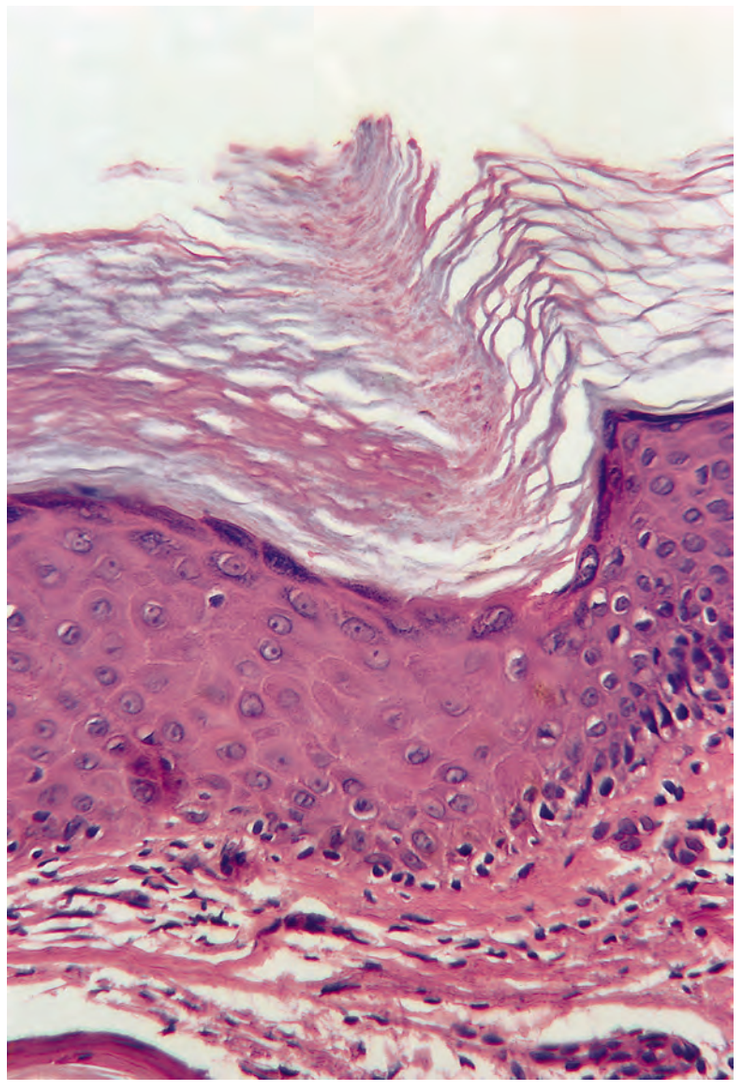

Figure 1.12 A cornoid lamella in porokeratosis. A thin column of parakeratotic cells overlies a narrow zone in which the granular layer is absent. (H&E)

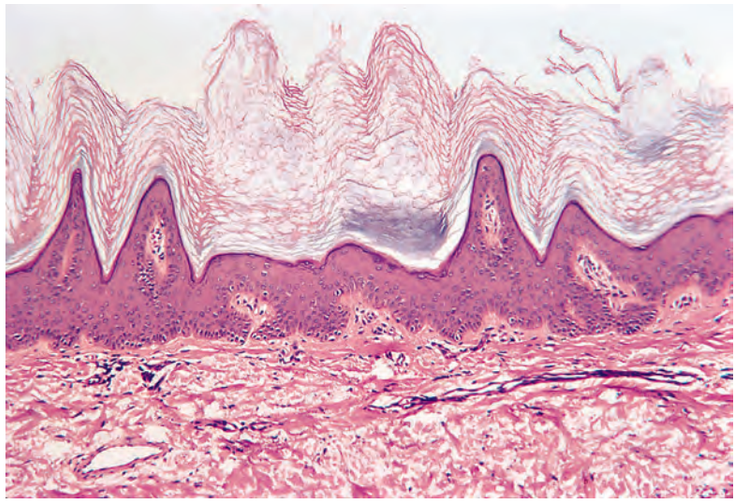

Figure 1.13 Papillomatosis ('church-spiring'). This is acrokeratosis verruciformis. (H&E)

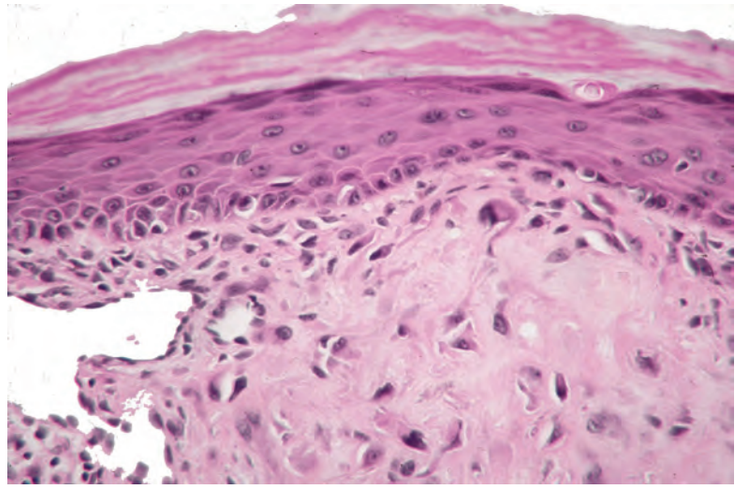

Figure 1.14 Angiofibroma. There are dilated vessels with intervening fibrosis and stellate cells. (H&E)

Table 1.8 Lesions showing papillomatosis

Seborrheic keratosis
Acrokeratosis verruciformis
Verruca vulgaris
Epidermodysplasia verruciformis
Verruca plana
Stucco keratosis
Tar keratosis
Arsenical keratosis
Solar keratosis
Acanthosis nigricans
Reticulated papillomatosis
Epidermal nevus
Verrucous carcinoma
Keratosis follicularis spinulosa
Multiple minute digitate keratoses
Hyperkeratosis lenticularis
Rubbed and scratched skin

Table 1.9 Conditions showing an angiofibromatous pattern

Adenoma sebaceum (tuberous sclerosis)
Angiofibromas in syndromes – MEN1, neurofibromatosis
Subungual and periungual fibroma
Acquired acral fibrokeratoma
Fibrous papule of the nose (and face)
Pearly penile papules
Familial myxovascular fibromas

a characteristic feature of porokeratosis and its clinical variants, it can be found as an incidental phenomenon in a range of inflammatory, hyperplastic, and neoplastic conditions of the skin.

PAPILLOMATOSIS ('CHURCH-SPIRING')

Papillomatosis refers to the presence of undulations or projections of the epidermal surface (**Fig. 1.13**). This may vary from tall 'steeple-like' projections to quite small, somewhat broader elevations of the epidermal surface. The term 'church-spiring' is sometimes used to refer to these changes. The various lesions showing papillomatosis are listed in **Table 1.8**.

ACRAL ANGIOFIBROMAS

The acral angiofibroma reaction pattern is characterized by an *increase in the number of small vessels, which is associated with perivascular and, sometimes, perifollicular fibrosis* (see p. 968). The fibrous tissue usually contains stellate cells (**Fig. 1.14**). The conditions showing this reaction pattern are listed in **Table 1.9**.

EOSINOPHILIC CELLULITIS WITH 'FLAME FIGURES'

In eosinophilic cellulitis with 'flame figures', there is *dermal edema with an infiltration of eosinophils and some histiocytes and scattered 'flame figures'* (**Fig. 1.15**). 'Flame figures' result from the adherence of amorphous or granular eosinophilic material to collagen bundles in the dermis. They are small, poorly circumscribed foci of apparent 'necrobiosis' of collagen, although they are eosinophilic rather than basophilic as seen in the usual 'necrobiotic' disorders.

Eosinophilic cellulitis with 'flame figures' can occur as part of a generalized cutaneous process known as Wells' syndrome (see p. 1132). This reaction pattern, which may represent a severe urticarial hypersensitivity reaction to various stimuli, can also be seen, rarely, in biopsies from arthropod reactions, other parasitic infestations, internal cancers, bullous pemphigoid, dermatitis herpetiformis, diffuse erythemas, and *Trichophyton rubrum* infections. The 'flame figures' of eosinophilic cellulitis resemble the Splendore–Hoeppli deposits that are sometimes found around parasites in tissues.

TRANSEPITHELIAL ELIMINATION

The term 'transepithelial elimination' was coined by Mehregan for a biological phenomenon whereby materials foreign to the skin are eliminated through pores between cells of the epidermis or hair follicle or are carried up between cells as a passive phenomenon, during

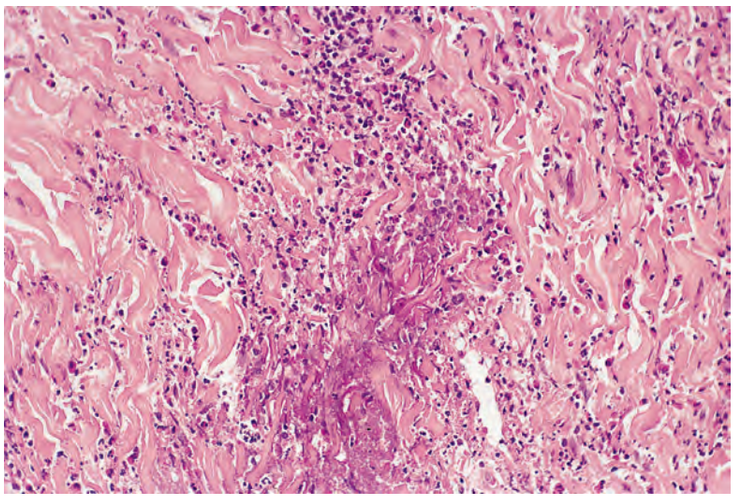

Figure 1.15 Eosinophilic cellulitis with flame figures. (H&E)

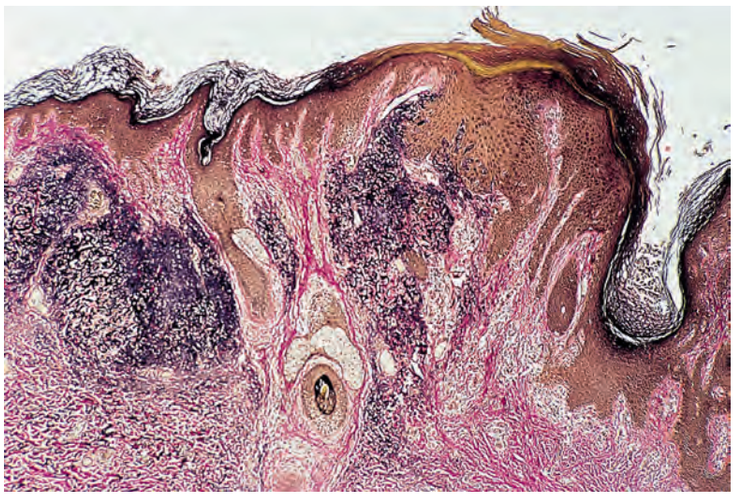

Figure 1.16 Transepithelial elimination of solar elastotic material is occurring through an enlarged follicular infundibulum. (Verhoeff–van Gieson)

maturation of the epidermal cells.[1] The validity of this hypothesis has been confirmed using an animal model.[2] The process of transepithelial elimination can be recognized in tissue sections by the presence of pseudoepitheliomatous hyperplasia or expansion of hair follicles (**Fig. 1.16**). These downgrowths of the epidermis or follicle usually surround the material to be eliminated, and the term 'epidermal vacuum cleaner' can be applied to them. Various tissues, substances, or organisms can be eliminated from the dermis in this way, including elastic fibers, collagen, erythrocytes, amyloid, calcium salts, bone, foreign material, inflammatory cells and debris, fungi, and mucin.[3–16] The various disorders (also known as 'perforating disorders') that may show transepithelial elimination are listed in **Table 1.10**.

An extension of this process is the **transdermal elimination** of fat. This occurs particularly after traumatic fat necrosis, but it rarely follows one of the panniculitides. Clinically, it presents as a 'discharging' lesion, but histologically, fat cells are often not found near the epidermis, suggesting that liquefied fat is involved in this discharge; it has presumably been removed during the processing of the specimen.

The apparent transepithelial elimination of a sebaceous gland has been reported.[17] This process was probably an artifact of tissue sectioning.

Table 1.10 Diseases in which transepithelial elimination may occur

Necrobiosis lipoidica
Necrobiotic xanthogranuloma
Perforating folliculitis
Pseudoxanthoma elasticum
Elastosis perforans serpiginosa
Reactive perforating collagenosis
Calcaneal petechiae ('black heel')
Amyloidosis
Chondrodermatitis nodularis helicis
Urate crystals
Calcinosis cutis
Osteoma cutis
Deep mycoses
Cutaneous tuberculosis
Blastomycosis-like pyoderma
Granuloma inguinale
Sarcoidosis
Foreign body granulomas
Exogenous pigment
Suture material
Lichen nitidus
Papular mucinosis
Acne keloidalis nuchae
Solar elastosis
Post-cryotherapy injury
Cutaneous tumors

PATTERNS OF INFLAMMATION

Four patterns of inflammation can be discerned in biopsies taken from the various inflammatory diseases of the skin: superficial perivascular inflammation, superficial and deep dermal inflammation, folliculitis and perifolliculitis, and panniculitis. Superficial band-like infiltrates are not included as a separate category because they are usually associated with the lichenoid reaction pattern (interface dermatitis) or the infiltrate is merely an extension of a superficial perivascular infiltrate.

SUPERFICIAL PERIVASCULAR INFLAMMATION

Superficial perivascular inflammation is usually associated with the spongiotic, psoriasiform, or lichenoid reaction patterns. Occasionally, diseases that are usually regarded as showing the spongiotic reaction pattern have only very mild spongiosis that may not always be evident on casual inspection of one level of a biopsy. This should be kept in mind when a superficial perivascular inflammatory reaction is present.

Causes of a superficial perivascular infiltrate, in the absence of spongiosis or another reaction pattern, include the following:

- Drug reactions
- Dermatophytoses
- Viral exanthems
- Chronic urticaria
- Erythrasma

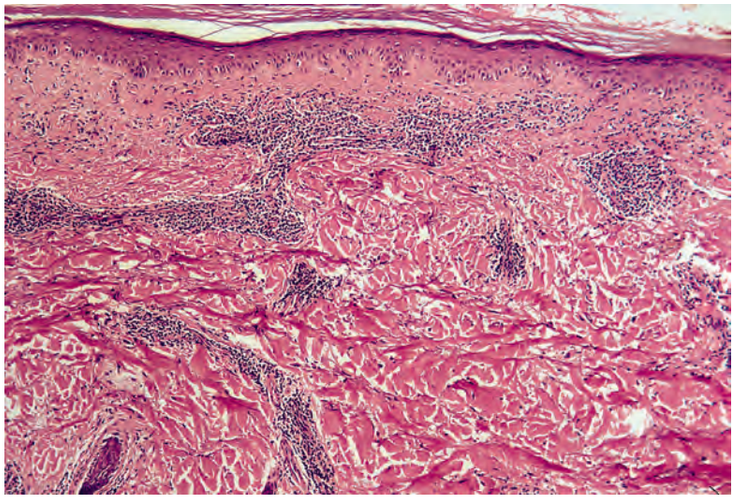

Figure 1.17 There is a superficial and deep perivascular infiltrate of lymphocytes. The presence of mild lichenoid changes suggests a diagnosis of lupus erythematosus. (H&E)

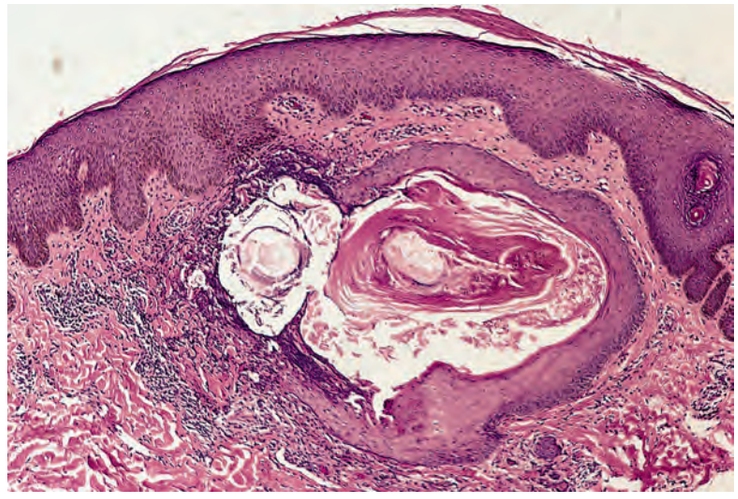

Figure 1.18 The acute folliculitis has ruptured with extension of the inflammatory infiltrate into the adjacent dermis. (H&E)

- Superficial annular erythemas
- Pigmented purpuric dermatoses
- Resolving dermatoses.

SUPERFICIAL AND DEEP DERMAL INFLAMMATION

Superficial and deep dermal inflammation may accompany a major reaction pattern, as occurs in discoid lupus erythematosus, in which there is a concomitant lichenoid reaction pattern, and also in photocontact allergic dermatitis, in which there is a spongiotic reaction pattern in addition to the dermal inflammation. This pattern of inflammation may also occur in the absence of any of the six major reaction patterns already discussed. The predominant cell type is usually the lymphocyte, but there may be a variable admixture of other cell types (Fig. 1.17). The often-quoted mnemonic of diseases causing this pattern of inflammation is the eight 'L' diseases – *l*ight reactions, *l*ymphoma (including pseudolymphomas), *l*eprosy, *l*ues (syphilis), *l*ichen striatus, *l*upus erythematosus, *l*ipoidica (includes necrobiosis lipoidica and incomplete forms of granuloma annulare), and *l*epidoptera (used incorrectly in the mnemonic to refer to arthropod bites and other parasitic infestations). To the eight 'L' diseases should be added 'DRUGS' – *drug* reactions, as well as *d*ermatophyte infections, *r*eticular erythematous mucinosis, *u*rticaria (chronic urticaria and the urticarial stages of bullous pemphigoid and herpes gestationis), *g*yrate erythemas (deep type), and *s*cleroderma (particularly the localized variants).

This list is obviously incomplete, but it covers most of the important diseases having this pattern of inflammation. For example, the vasculitides and various granulomatous diseases have superficial and deep inflammation in the dermis, but they have been excluded from the mnemonics because they constitute major reaction patterns. It is always worth keeping in mind these mnemonics when a superficial and deep infiltrate is present in tissue sections.

FOLLICULITIS AND PERIFOLLICULITIS

Inflammation of the hair follicle (folliculitis) usually extends into the adjacent dermis, producing a perifolliculitis (Fig. 1.18). For this reason, these two patterns of inflammation are considered together. There are several ways of classifying the various folliculitides, the most common being based on the anatomical level of the follicle (superficial or deep) that is involved. This distinction is not always clear-cut, and in some cases of folliculitis due to an infectious agent, the follicle may be inflamed throughout its entire length. The folliculitides are discussed in further detail in Chapter 15.

Infectious agents are an important cause of folliculitis and perifolliculitis, and diseases showing this pattern of inflammation are sometimes subclassified into 'infective' and 'non-infective' groups. If this etiological classification is used in conjunction with the anatomical level of the follicle most affected by the inflammation, four groups of folliculitides are produced. The important diseases in each of these groups are listed in parentheses:

1. *Superficial infective folliculitis* (impetigo, some fungal infections, herpes simplex folliculitis, and folliculitis of secondary syphilis)
2. *Superficial non-infective folliculitis* (infundibulofolliculitis, actinic folliculitis, acne vulgaris (?), acne necrotica, and eosinophilic pustular folliculitis)
3. *Deep infective folliculitis* (kerion, favus, pityrosporum folliculitis, Majocchi's granuloma, folliculitis decalvans, furuncle, and herpes simplex folliculitis)
4. *Deep non-infective folliculitis* (hidradenitis suppurativa, dissecting cellulitis of the scalp, acne conglobata, and perforating folliculitis).

In sections stained with H&E, the division into superficial or deep folliculitis can usually be made, except in cases with overlap features. Further subdivision into infective and non-infective types may require the use of special stains for organisms. It should be remembered that the involved hair follicle may not be present in a particular histological section, and serial sections may need to be studied. An apparent 'uneven vasculitis' (involving a localized part of the biopsy) is a clue to the presence of a folliculitis in a deeper plane of section.

PANNICULITIS

Inflammatory lesions of the subcutaneous fat can be divided into three distinct categories: *septal panniculitis*, in which the inflammation is confined to the interlobular septa of the subcutis; *lobular panniculitis*, in which the inflammation involves the entire fat lobule and often the

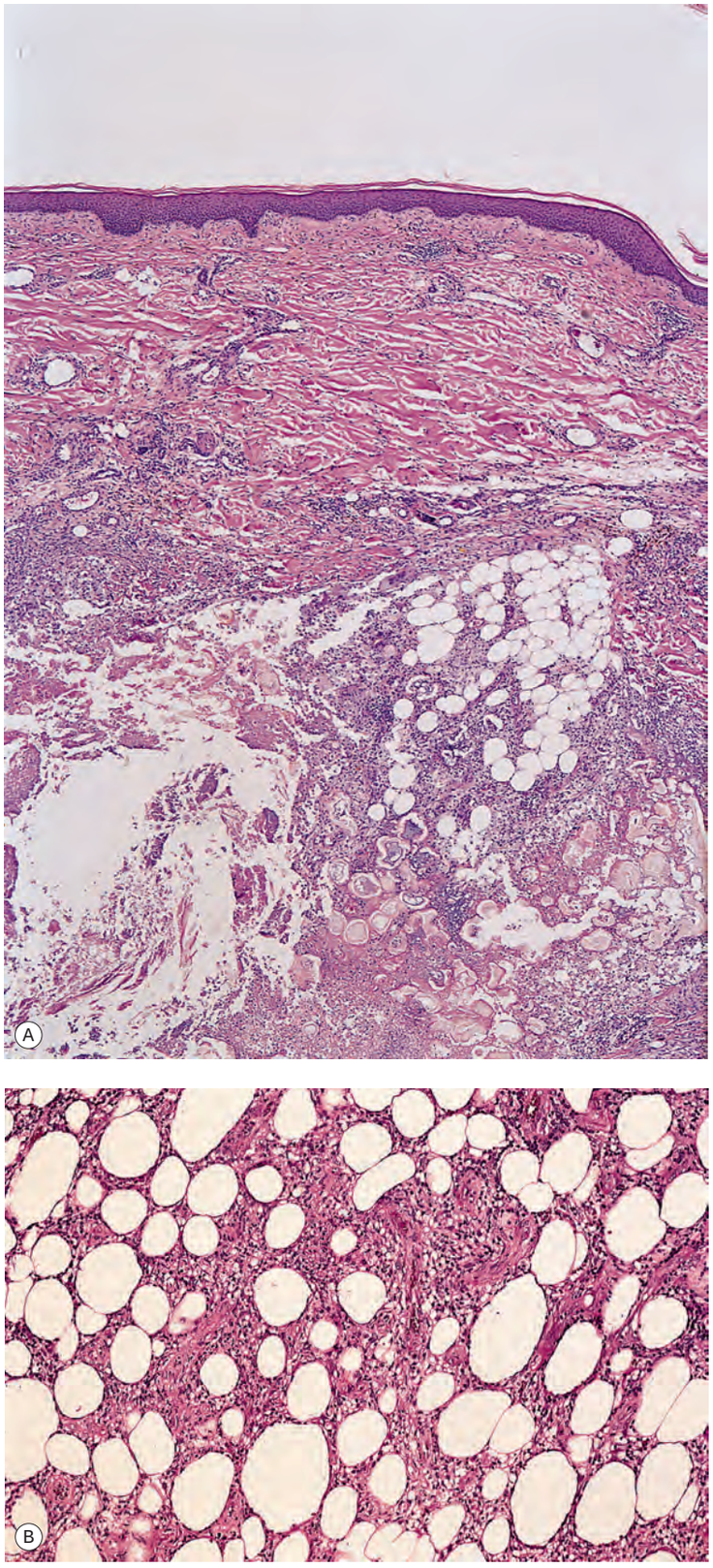

Figure 1.19 **(A) A panniculitis** of lobular type is present in a case of pancreatic panniculitis. **(B) Another example of a lobular panniculitis** in a patient with erythema induratum–nodular vasculitis. (H&E)

Table 1.11 Diseases causing a panniculitis

Septal panniculitis
Erythema nodosum
Necrobiosis lipoidica
Scleroderma
Factitial panniculitis (some)
Nephrogenic systemic fibrosis
Cellulitis
Microscopic polyangiitis
Hydroa vacciniforme
Apomorphine infusion
Cryoglobulinemia
Whipple's disease
Cytomegalovirus infection
α_1-Antitrypsin deficiency (rare cases)
Lobular panniculitis
Erythema induratum – nodular vasculitis
Subcutaneous fat necrosis of the newborn
Sclerema neonatorum
Cold panniculitis
Weber–Christian disease
α_1-Antitrypsin deficiency
Cytophagic histiocytic panniculitis
Panniculitis-like T-cell lymphoma
Atypical lobular panniculitis
Pancreatic panniculitis
Lupus panniculitis
Connective tissue panniculitis
Post-steroid panniculitis
Lipodystrophy syndromes
Membranous lipodystrophy
Lipodermatosclerosis
Factitial panniculitis
Traumatic fat necrosis
Infective panniculitis
Non-infective neutrophilic panniculitis
Eosinophilic panniculitis
Panniculitis secondary to large vessel vasculitis
Cutaneous polyarteritis nodosa
Superficial migratory thrombophlebitis

septa as well; and *panniculitis secondary to vasculitis involving large vessels in the subcutis*, in which the inflammation is usually restricted to the immediate vicinity of the involved vessel (**Fig. 1.19**). The various panniculitides are listed in **Table 1.11**. They are discussed further in Chapter 17.

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The complete reference list can be found on the companion Expert Consult website at www.expertconsult.inkling.com.

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2 Diagnostic clues

In the previous chapter, an orderly approach to the diagnosis of inflammatory skin lesions was discussed. This chapter records in list form some useful points that may assist in reaching a correct diagnosis. Many of the clues that follow produce diagnostic lists that are not necessarily related to tissue reaction, etiology, or pathogenesis.

Some of the clues that follow are original observations; many have been around for decades. An acknowledgment should be made here of the work of Bernard Ackerman, who has contributed more 'clues' to diagnostic dermatopathology than anyone else.

Like all 'shortcuts', the following 'clues' must be used with caution. They are not absolute criteria for diagnosis, and they are not invariably present at all stages of a disease. An attempt has been made to group the clues into several sections.

FEATURES OF PARTICULAR PROCESSES

SIGNS OF PHOTOSENSITIVITY (Fig. 2.1)

- Dilated vessels in the upper dermis
- Stellate fibroblasts/dendrocytes
- Deep elastotic fibers
- Deep extension of the infiltrate
- Epidermal 'sunburn' cells.

Note: The duration of the process and the underlying nature of the light reaction will influence the response. Only one or two features may be present, for example, sunburn cells (apoptotic keratinocytes) are confined to phototoxic and photosensitive drug eruptions.

SIGNS OF RUBBING/SCRATCHING (Fig. 2.2)

Acute, severe:	Pale pink epidermis, sometimes with loss of cell borders; pinpoint erosions or larger ulcers; fibrin below the epidermis
Chronic, persistent:	Psoriasiform epidermal hyperplasia; vertical streaks of collagen in the papillary dermis; stellate fibroblasts/dendrocytes; fibroplasia of varying amounts; enlarged follicular infundibula (as prurigo nodularis commences); compact orthokeratosis.

SUBTLE CLUES TO DRUG REACTIONS

- Superficial dermal edema
- Activated lymphocytes
- Eosinophils and/or plasma cells
- Red cell extravasation
- Endothelial swelling of vessels
- Exocytosis of lymphocytes
- Apoptotic keratinocytes.

The changes present will mirror the clinical types of reaction. In morbilliform reactions, lymphocytes extend into the lower epidermis and the apoptotic keratinocytes are in the basal layer.

CLUES TO ELASTIC TISSUE ALTERATIONS

- Small blue coiled/clumped fibers (pseudoxanthoma elasticum)
- Wavy epidermis (particularly in children)
- Elastophagocytosis
- Dispersed neutrophils (early cutis laxa)
- Unusually thickened collagen (connective tissue nevus).

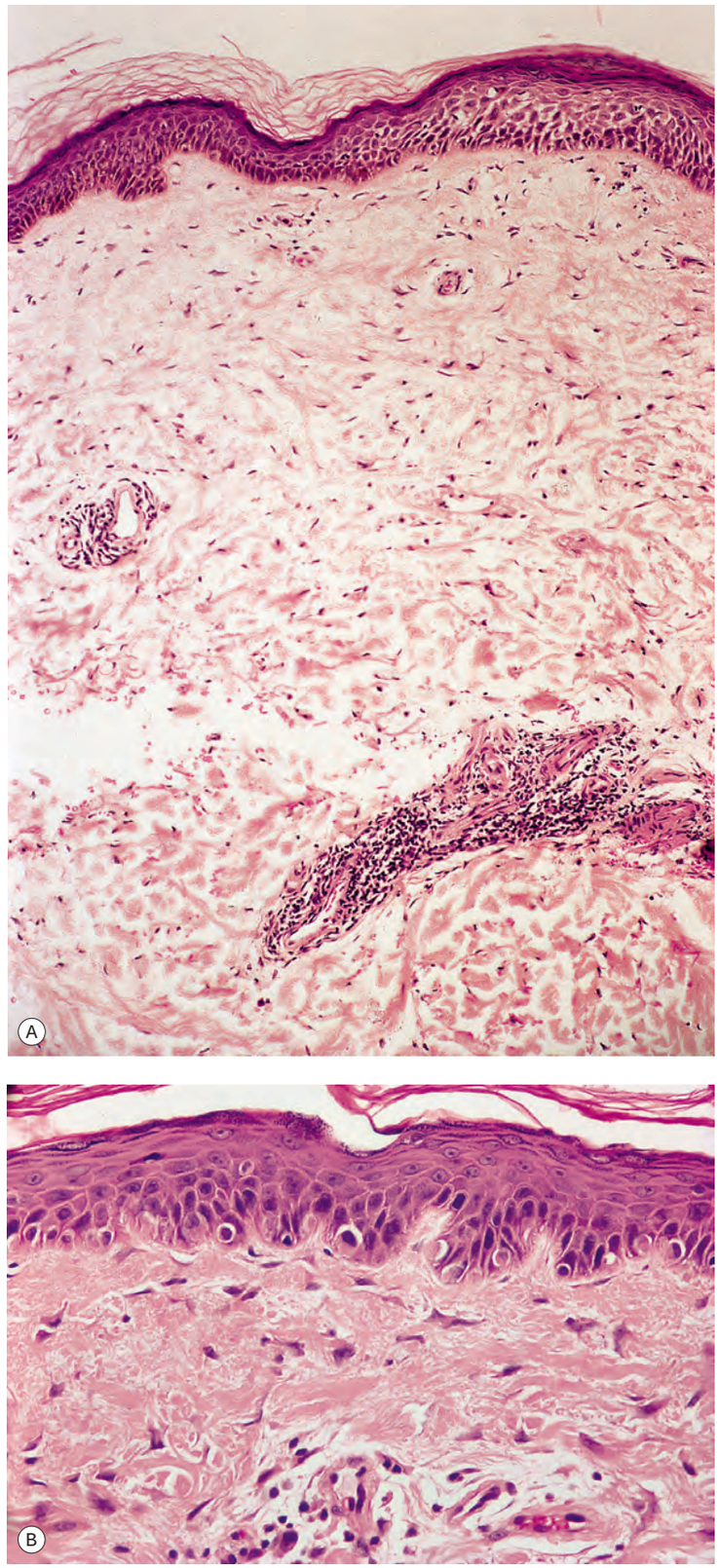


Figure 2.1 Photosensitivity reaction. (A) Note the mild telangiectasia, scattered stellate cells, deep extension of the infiltrate, and mild deep solar elastosis. **(B)** Note the stellate cells. (H&E)

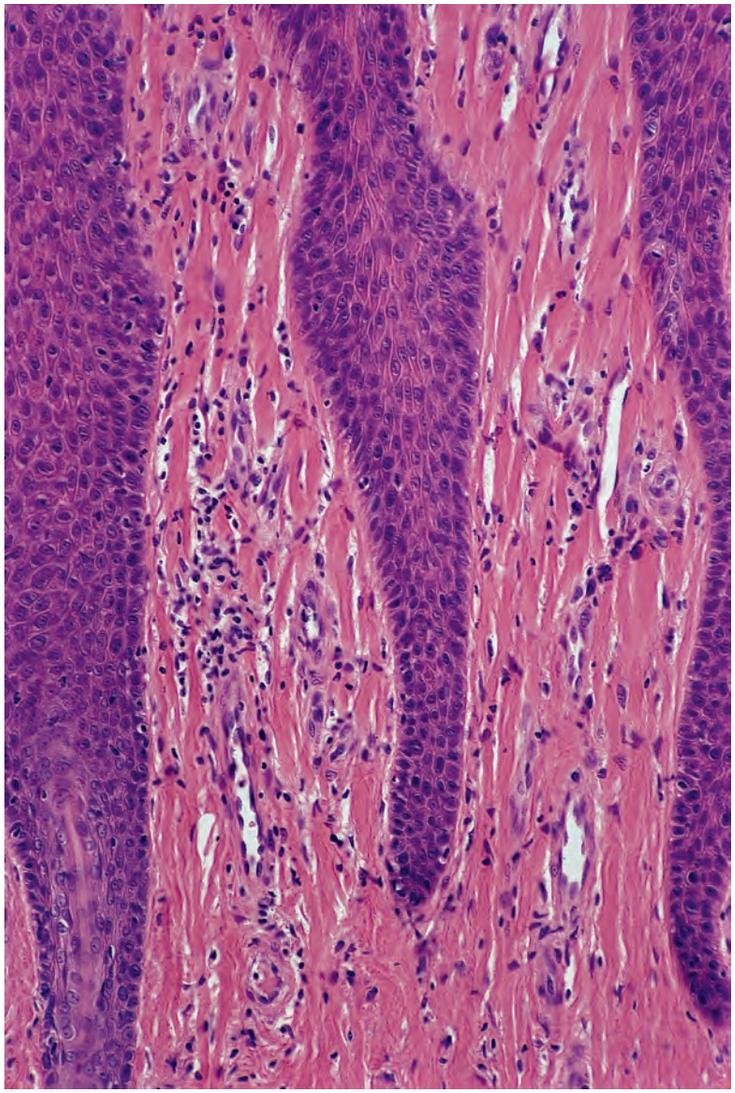


Figure 2.2 Chronic rubbing leading to vertical collagen in the papillary dermis and psoriasiform hyperplasia of the epidermis. (H&E)

CLUES TO DEFICIENCY STATES

- Confluent parakeratosis
- Superficial epidermal necrosis and/or pallor
- Mild psoriasiform hyperplasia
- Hemorrhage (in pellagra and mixed deficiencies).

CLUES TO FUNGAL INFECTIONS (Fig. 2.3)

Basically, these features should prompt the performance of a PAS stain. Many simulants exist.

- Compact orthokeratosis with no other explanation
- Layering of epidermal cornification ('sandwich sign')
- Neutrophils in the epidermis/stratum corneum
- Spongiosis, particularly palmoplantar
- Suppurative folliculitis.

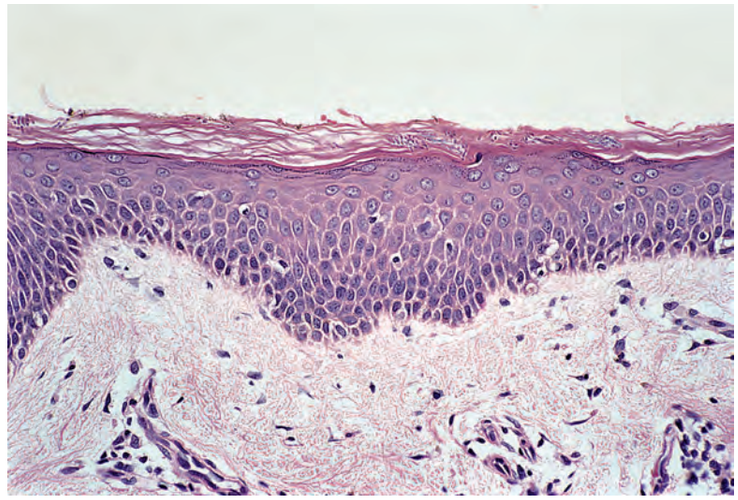


Figure 2.3 Dermatophyte. The fungal elements are present in the region with compact orthokeratosis. Note the adjacent normal 'basket-weave' pattern. (H&E)

SUBTLE CLUES TO A FOLLICULITIS (Fig. 2.4)

These signs refer to a likely folliculitis at deeper levels of the biopsy.

- Neutrophils on top of the stratum corneum
- Neutrophils at the edge of the tissue section
- Uneven vasculitis (centered in one small area) – miliaria may do the same
- Focal splaying of neutrophils and dust in mid dermis.

'LAST WEEK'S SIGN' (Fig. 2.5)

This refers to a dermatosis, no longer active, that is 'playing itself out'. It was presumably more active some days earlier.

- Parakeratosis overlying basket-weave orthokeratin (the key feature)
- Mild hyperplasia of the epidermis
- Mild dermal inflammation.

LAGGING HISTOLOGY

This refers to several conditions in which the clinical appearances may be striking in comparison to the histology.

- Sclerodermoid GVHD may have 'rock-hard skin' but only subtle collagen deposition
- Cicatricial alopecia can be similar
- Urticaria: Histology underestimates the edema because of dehydration during tissue processing
- Prurigo nodularis: There may be clinical nodules but no histological swollen infundibula, only psoriasiform hyperplasia of lichen simplex chronicus
- Pauci-cellular photodermatoses: There may be striking clinical changes but only telangiectasia and sparse inflammatory cells on histology.

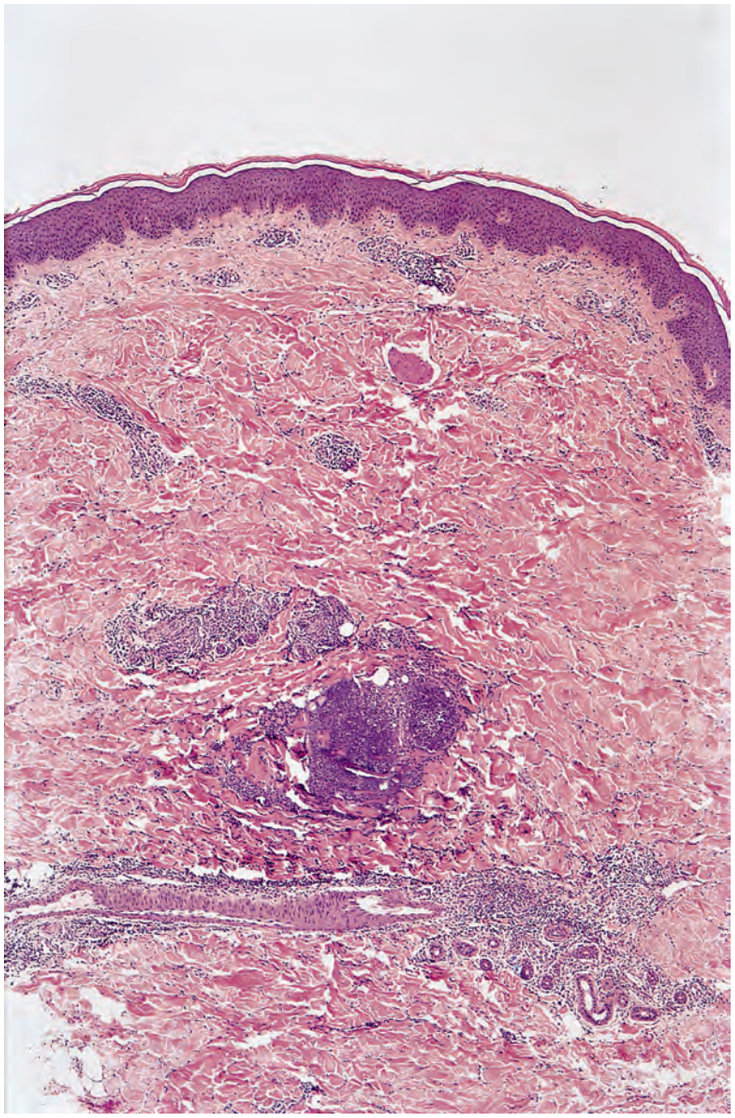


Figure 2.4 Folliculitis. There is deep dermal inflammation and an 'uneven vasculitis' more superficially. A ruptured and inflamed follicle was present on deeper levels. (H&E)

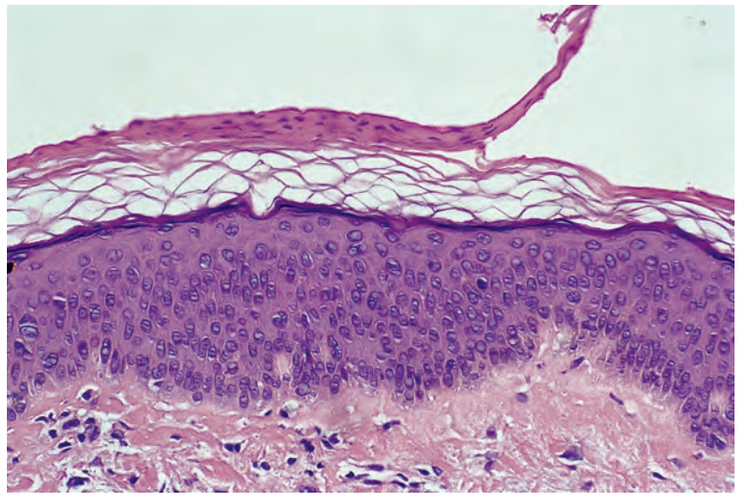


Figure 2.5 'Last week's sign'. The return to the production of normal basket-weave keratin beneath a layer of parakeratosis suggests there is little ongoing activity in this region. (H&E)

HISTOLOGICAL FEATURES – WHAT DO THEY SUGGEST?

SUPERFICIAL AND DEEP INFLAMMATION (Fig. 2.6)

The presence of a superficial and deep inflammatory cell infiltrate within the dermis should trigger the mnemonic '8Ls + DRUGS'.

8Ls

- Light reactions
- Lymphoma
- Leprosy
- Lues
- Lichen striatus
- Lupus erythematosus
- Lipoidica (necrobiosis)
- Lepidoptera (and other arthropods)

Drugs

- Dermatophyte
- Reticular erythematous mucinosis
- Urticarial stages (bullous pemphigoid)
- Gyrate erythemas
- Scleroderma (localized)
- And, of course, drug reactions

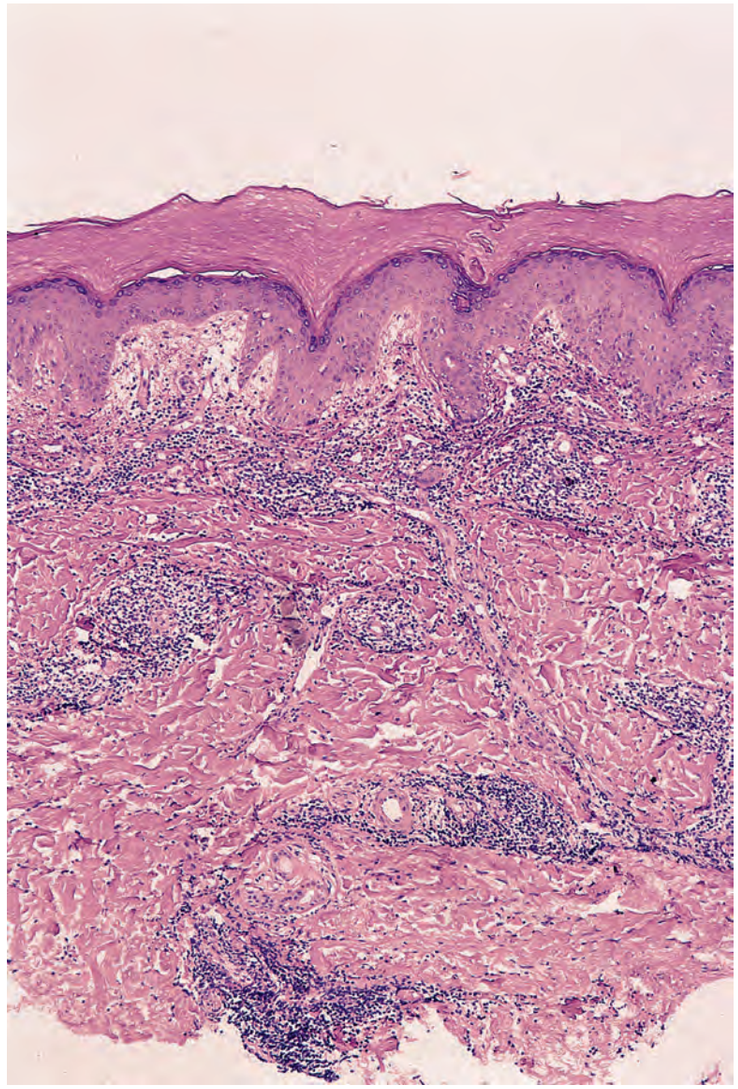


Figure 2.6 A superficial and deep dermal infiltrate. This is one of the 'L' diseases – polymorphic *l*ight eruption. (H&E)

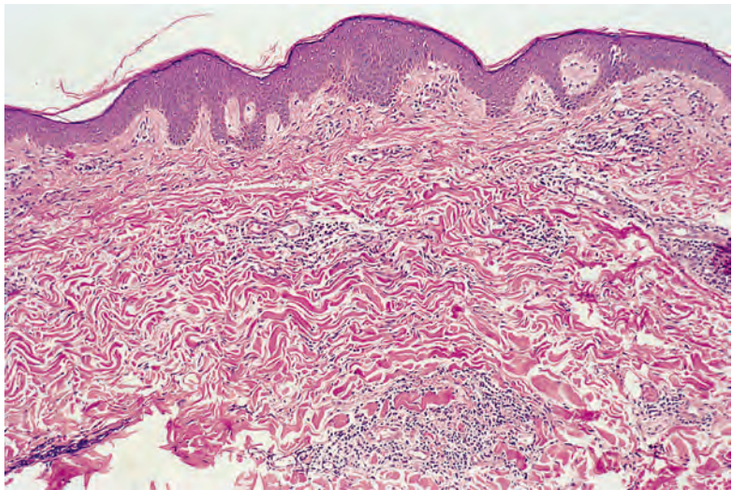


Figure 2.7 A 'busy' dermis. There is hypercellularity in this case of interstitial granulomatous drug reaction. (H&E)

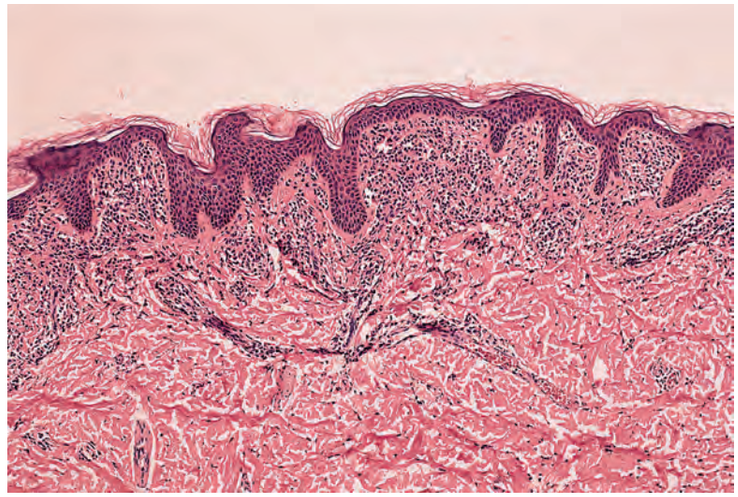


Figure 2.8 The papillary dermis is filled. This is mastocytosis. (H&E)

A 'BUSY' DERMIS (Fig. 2.7)

'Busy' refers to a dermis that appears focally hypercellular on scanning magnification and is not usually due to the usual inflammatory infiltrates.

- Incomplete form of granuloma annulare
- Interstitial granulomatous dermatitis
- Interstitial granulomatous drug reaction
- Resolving vasculitis (increased mucin also)
- Chronic photodermatoses
- Folliculitis – at deeper levels (cells are neutrophils and dust)
- Subtle breast carcinoma recurrence
- Desmoplastic melanoma (also perivascular lymphocytes)
- Kaposi's sarcoma (early stage).

ABSENT STRATUM CORNEUM

- Staphylococcal scalded skin syndrome
- Pemphigus foliaceus
- Peeling skin syndrome
- Psoriatic erythroderma (psoriasiform hyperplasia present)
- Artifacts.

FILLED PAPILLARY DERMIS (Fig. 2.8)

The low power impression is that of a variably hypercellular papillary dermis. Excluded from consideration are nodular and diffuse infiltrates also involving the reticular dermis. The 'LUMP' mnemonic covers most cases: *l*ichenoid, *u*rticaria pigmentosa, *m*ycosis fungoides, *p*igmented purpuric dermatoses. Expressed differently they are as follows:

- Most of the lichenoid tissue reactions
- Pigmented purpuric dermatoses
- Cutaneous T-cell lymphoma
- Parapsoriasis (if not included above)
- Some mastocytomas
- Early lichen sclerosus et atrophicus.

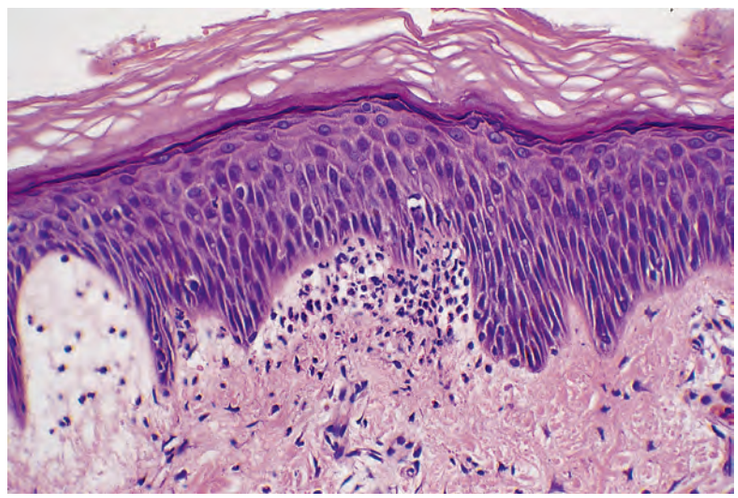


Figure 2.9 Dermal papillary microabscess. This is dermatitis herpetiformis. (H&E)

PAPILLARY MICROABSCESSES (Fig. 2.9)

- Dermatitis herpetiformis
- Linear IgA disease
- Cicatricial pemphigoid
- Localized cicatricial pemphigoid
- Bullous lupus erythematosus
- Epidermolysis bullosa acquisita
- Drugs
- Hypersensitivity vasculitis (rare)
- Rheumatoid neutrophilic dermatosis
- Pemphigoid gestationis (eosinophils)
- Deep lamina lucida pemphigoid
- Generalized exanthematous pustulosis (rare).

SPARSE PERIVASCULAR NEUTROPHILS

In some conditions, neutrophils are relatively sparse or less conspicuous than in vasculitis, a neutrophilic dermatosis or cellulitis.

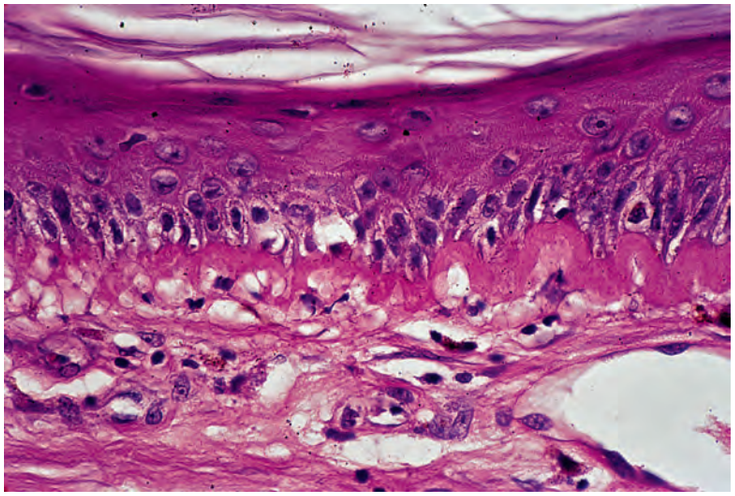


Figure 2.10 Thickened basement membrane and mild basal vacuolar change. This is an example of systemic lupus erythematosus. (H&E)

- Erythema marginatum
- Still's disease
- Neutrophilic urticaria
- Mild periodic fever syndromes
- Early or subsiding neutrophilic dermatoses
- Neutrophilic erythemas of infancy
- Some flea bites.

THICKENED BASEMENT MEMBRANE (Fig. 2.10)

- Lupus erythematosus
- Dermatomyositis (less so)
- Lichen sclerosus et atrophicus.

MID-DERMAL INFILTRATE AND MUCIN (Fig. 2.11)

- Cutaneous lupus erythematosus
- Reticular erythematous mucinosis (REM)
- Jessner's lymphocytic infiltrate.

Other signs will usually allow these diagnoses, but sometimes REM will present with very little deep infiltrate. Biopsies appear to have a 'mid-dermal plexus'. Dermatomyositis can have mucin, but the infiltrate is only superficial. Perifollicular mucin can be seen in Carney's complex. REM and Jessner's infiltrate (no longer used) are both patterns of expression of cutaneous lupus erythematosus.

EPIDERMOTROPISM AND EXOCYTOSIS (Fig. 2.12)

The terms 'epidermotropism' and 'exocytosis' are often used interchangeably. It is best to restrict them as follows:

Exocytosis: Random emigration of inflammatory cells through the epidermis; some cells will reach the surface. It is common in inflammatory dermatoses. In the spongiotic tissue reaction, it may be a striking feature in nummular dermatitis and spongiotic drug reactions

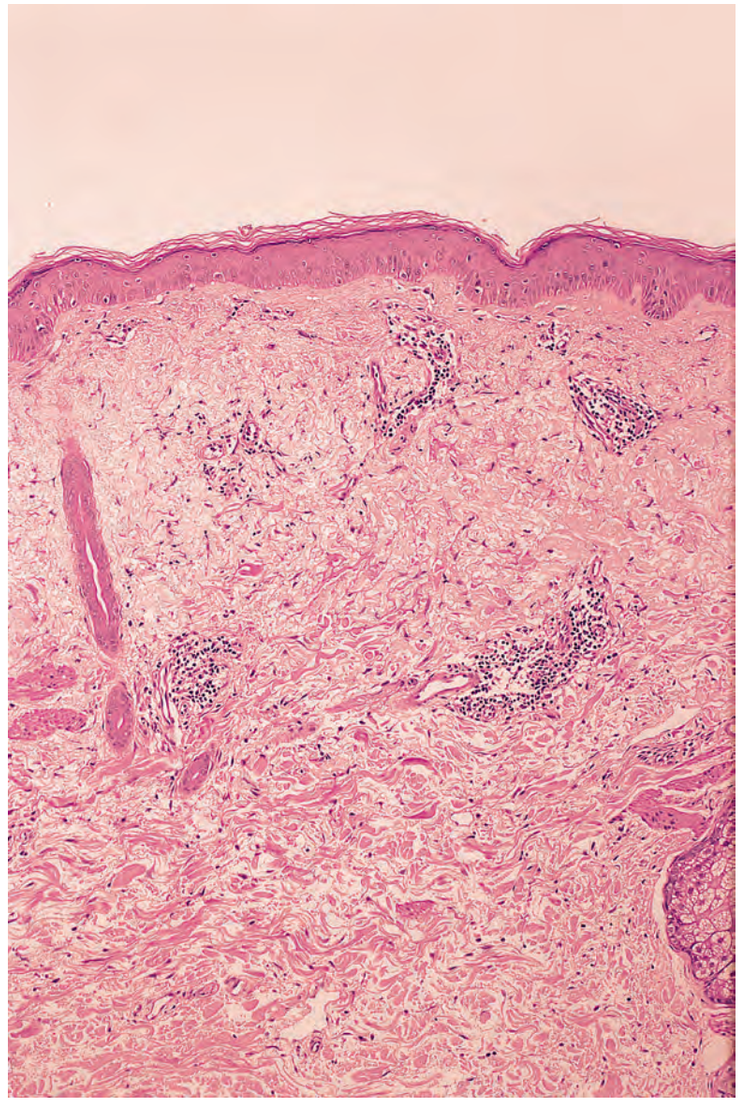


Figure 2.11 A 'mid-dermal plexus' with perivascular inflammation is present. Lupus and reticular erythematous mucinosis (REM) can do this (they may be the one condition). The mucin is difficult to appreciate. (H&E)

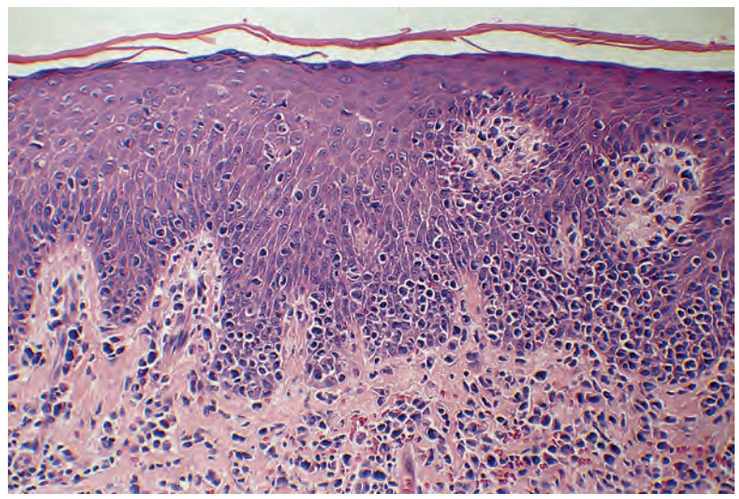


Figure 2.12 Epidermotropism. The cells are confined to the lower one-third to one-half of the epidermis. (H&E)

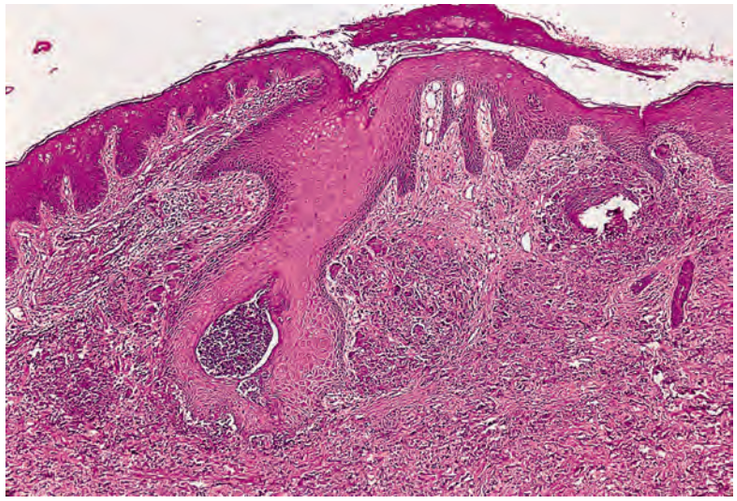


Figure 2.13 Epidermal 'vacuum cleaner'. The acanthotic downgrowth serves as a site for transepidermal elimination of elastotic material in this case of perforating pseudoxanthoma elasticum. (H&E)

Epidermotropism: Refers to directed emigration of lymphocytes; it usually involves only the lower one-third to half of the epidermis. The cells have a tendency to aggregate. There is little, if any, accompanying spongiosis. It is a feature of mycosis fungoides.

THE EPIDERMAL/FOLLICULAR 'VACUUM CLEANER' (Fig. 2.13)

The epidermal/follicular 'vacuum cleaner' is the author's term for the irregular epidermal hyperplasia ± enlarged follicular infundibula, associated with the transepidermal elimination of material from the dermis. It can be subtle following cryotherapy to sun-damaged skin; it may be the cause of a persistent lesion at the site, often mistaken as a clinical recurrence.

PARAKERATOSIS AS A HELPFUL SIGN

Lipping: See below

Spongiosis: Pityriasis rosea, erythema annulare centrifugum, seborrheic dermatitis, other spongiotic diseases

Neutrophils: Psoriasis (neutrophils in 'summits' of mounds), seborrheic dermatitis, dermatophyte infection, necrolytic erythema, secondary bacterial infection

In tiers: Porokeratosis, verruca vulgaris, palmoplantar psoriasis

With interface change: Lichenoid drug, lichen planus-like keratosis, pityriasis lichenoides, lupus erythematosus (more often orthokeratosis)

Overlying orthokeratosis: Healing lesion or intermittent activity, particularly a spongiotic process

Alternating: Alternating orthokeratosis and parakeratosis in a horizontal direction is seen in ILVEN, and actinic keratosis, and in a horizontal and vertical direction in pityriasis rubra pilaris

Broad thick zones: Psoriasis, glucagonoma and deficiency states (epidermal pallor is not invariable), pityriasis lichenoides, granular parakeratosis.

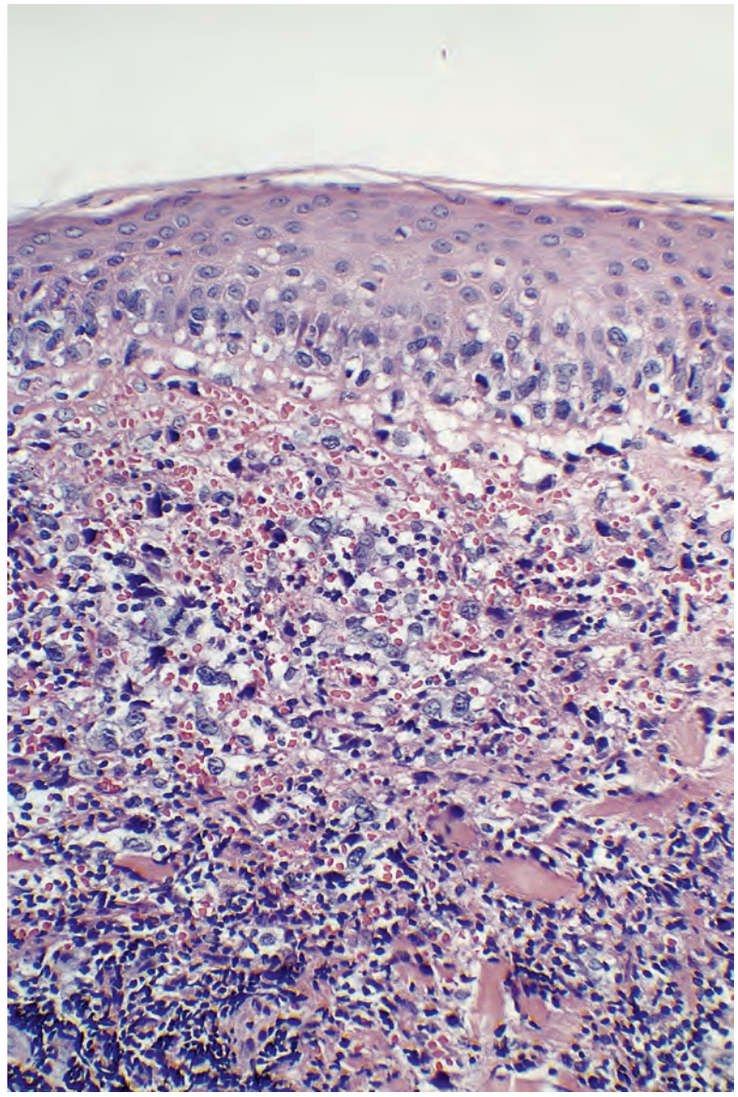


Figure 2.14 'Chunks of coal'. Cells with large, dark, hyperchromatic nuclei are present in the dermis in this case of lymphomatoid papulosis. (H&E)

PARAKERATOTIC FOLLICULAR LIPPING

- Seborrheic dermatitis
- Pityriasis rubra pilaris (follicular lesions)
- Spongiotic processes, or psoriasis, on the face. The large number of follicles on the face means that they are more likely to be involved incidentally in any condition with parakeratosis.

'CHUNKS OF COAL' (Fig. 2.14)

Large atypical lymphoid cells within a heavy mixed infiltrate occur in lymphomatoid papulosis. The cells have been likened to 'chunks of coal'.

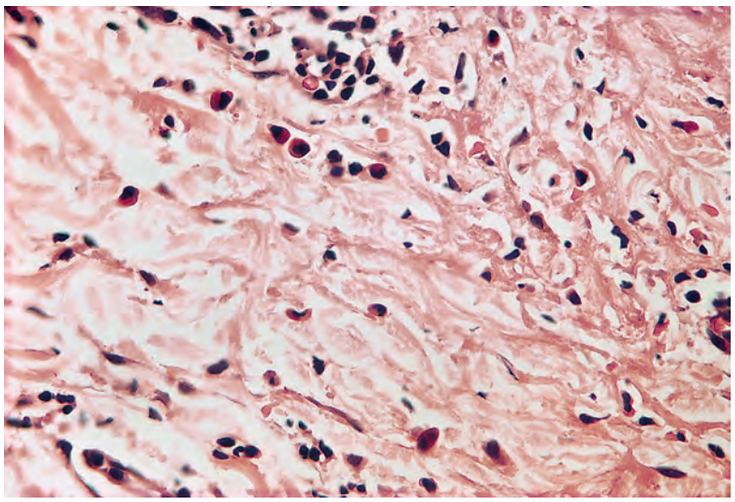


Figure 2.15 Interstitial eosinophils in an insect bite reaction. (H&E)

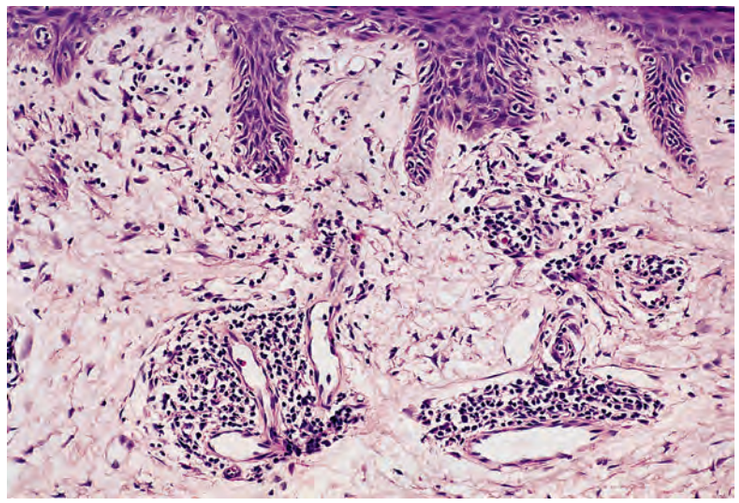


Figure 2.16 The 'bare underbelly' sign. Note the paucity of lymphocytes on the undersurface of the superficial vascular plexus. (H&E)

INTERSTITIAL EOSINOPHILS (Fig. 2.15)

'Interstitial eosinophils' refers to the presence of eosinophils between collagen bundles and away from vessels. Perivascular eosinophils are also present.

- Arthropod bites
- Cnidarian contact
- Other parasite infestations
- Drug reactions
- Toxic erythema of pregnancy
- Annular erythemas of infancy
- Wells' syndrome
- Dermal hypersensitivity
- Hypereosinophilic syndrome
- Urticaria
- Urticarial stages of bullous pemphigoid, pemphigoid gestationis
- Internal malignancy (rare).

Large numbers of eosinophils in suspected bite reactions suggest scabies or a hypersensitive state to the arthropod. Prebullous pemphigoid also has numerous eosinophils.

'BOTTOM-HEAVY' INFILTRATES

Dense lymphoid infiltrates may be found in the lower dermis in the following circumstances:

- Cutaneous lymphoma
- Herpes folliculitis
- Hidradenitis suppurativa (mixed infiltrate + scarring).

THE 'BARE UNDERBELLY' SIGN (Fig. 2.16)

In some cases of mycosis fungoides, the lymphocytes are present on the upper (epidermal) side of the superficial vascular plexus with few, if any, on the undersurface. This is possibly a reflection of their directed migration to the epidermis. It is an unreliable sign, but a striking one in some cases.

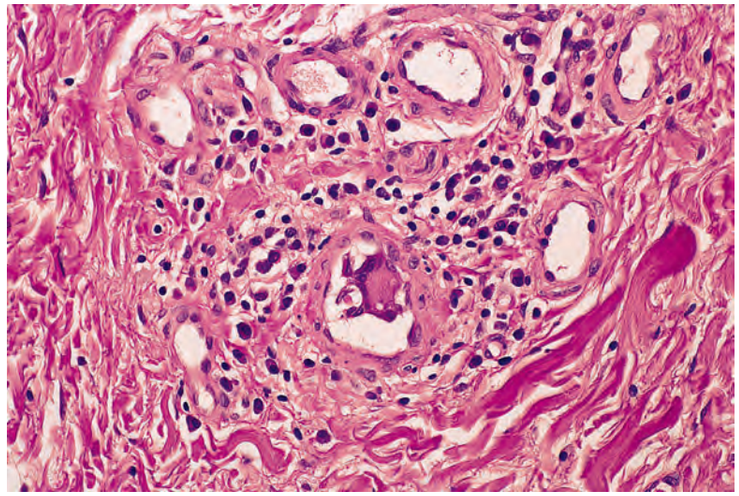


Figure 2.17 An intraluminal giant cell. The patient had chronic infections of the genital and inguinal region. (H&E)

INTRALUMINAL GIANT CELLS/HISTIOCYTES (Fig. 2.17)

- Melkersson–Rosenthal syndrome
- Recurrent genitocrural infections
- Cutaneous histiocytic lymphangitis (angioendotheliomatosis)
- Rosai–Dorfman disease.

INTRAVASCULAR LEUKOCYTES

Leukocytes (eosinophils and/or neutrophils) are often present in the lumen of small vessels in the upper dermis in urticaria, even in the absence of accompanying vasculitis, and in lymphomatoid papulosis.

HIGH APOPTOTIC (DYSKERATOTIC) KERATINOCYTES (Fig. 2.18)

Presumptive apoptotic keratinocytes (the author has not stained them or examined them ultrastructurally in most entities listed) may occur in the spinous layer in the following:

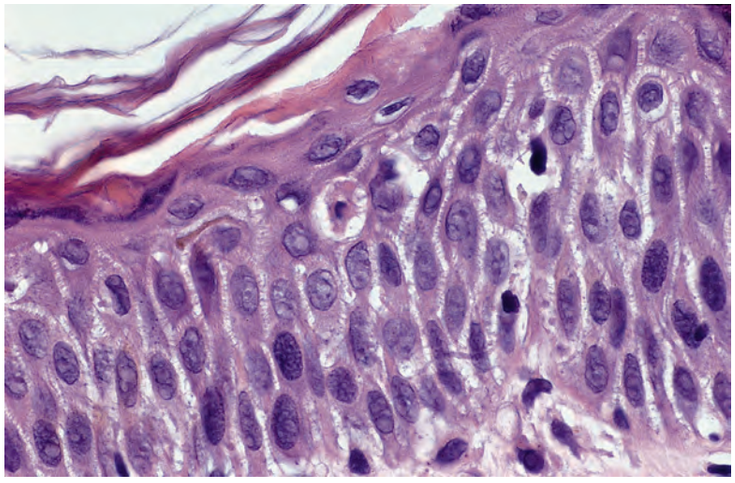


Figure 2.18 High apoptotic keratinocytes in a drug reaction. (H&E)

- Lichenoid tissue reaction – true 'interface-obscuring' subtype
- Drug reactions
- Light reactions
- Resolving viral and putative viral lesions
- AIDS-related sebopsoriasis
- Incontinentia pigmenti (second stage)
- Tumors (e.g., Bowen's disease)
- Rarely in normal skin and other inexplicable circumstances
- Near an excoriation
- Glucagonoma syndrome
- Acrodermatitis enteropathica
- Bazex's syndrome.

VERTICAL COLLAGEN BUNDLES

Vertically oriented collagen bundles in the *reticular* dermis (usually combined with other bundles in random array) are seen in the following:

- Collagenous and elastotic plaques of the hand
- Digital fibromatosis of childhood
- Acral fibrokeratomas.

LOOSE PINK FIBRILLARY COLLAGEN (Fig. 2.19)

If such tissue is surrounded by a granulomatous rim with foreign body giant cells, this is probably tophaceous gout in which the crystals have dissolved out in aqueous solutions.

EXTRAVASATED ERYTHROCYTES

- Vasculitides of all types
- Pigmented purpuric eruptions (included above)
- Certain drug eruptions
- Some viral, rickettsial infections, septicemia and erysipelas
- Some arthropod reactions
- Pityriasis rosea (often into basal epidermis)
- Bleeding diatheses – purpura, DIC
- Scurvy
- Kaposi's sarcoma

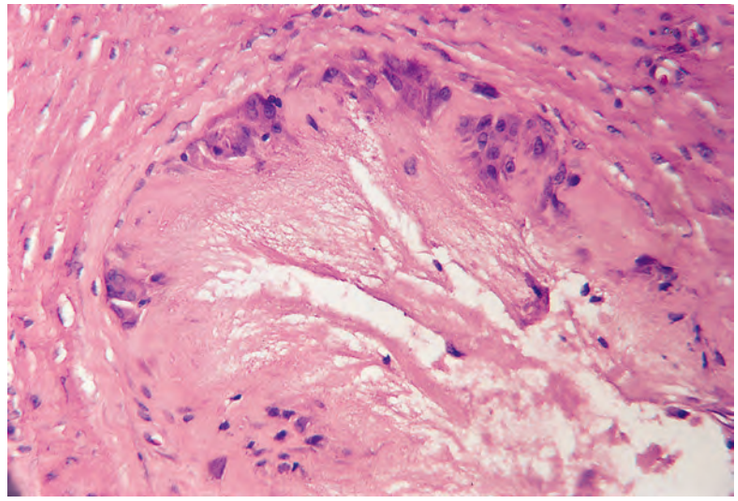


Figure 2.19 Giant cells surround eosinophilic material in this tophaceous gout that was fixed in formalin, dissolving out the urate crystals. (H&E)

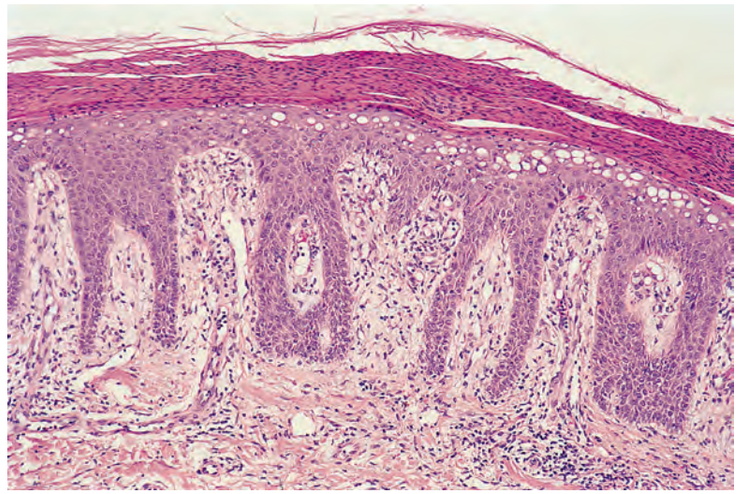


Figure 2.20 Pale cells are present in the upper epidermis in this case of glucagonoma syndrome. (H&E)

- Lichen sclerosus et atrophicus
- Biopsy trauma
- Trichotillomania
- Stasis dermatitis
- Porphyria cutanea tarda (in blister)
- Discoid lupus erythematosus.

PALLOR OF EPIDERMAL CELLS (Fig. 2.20)

- Pellagra
- Acrodermatitis enteropathica
- Glucagonoma syndrome
- Hartnup disease
- Deficiency of M-subunit, lactate dehydrogenase
- Acroerythema
- Spongiotic diseases (variable)
- Clear cell acanthoma
- Clear (pale) cell acanthosis

- Clear cell papulosis
- Pagetoid dyskeratosis
- Colloid keratosis.

Note: This list could include other conditions, but they are usually diagnosed by other clues (e.g., lichen planus, pityriasis lichenoides chronica, and orf).

CLEAR CELL TUMORS

Epidermal-derived

- Clear cell acanthoma
- Bowen's disease
- Basal cell carcinoma
- Squamous cell carcinoma.

Adnexal tumors

- Paget's disease
- Clear cell syringoma
- Clear cell syringofibroadenoma
- Clear cell dermal duct tumor
- Clear cell hidradenoma (apocrine hidradenoma)
- Clear cell hidradenocarcinoma (apocrine hidradenocarcinoma)
- Clear cell eccrine carcinoma
- Clear cell porocarcinoma
- Clear cell myoepithelioma
- Clear cell trichoblastoma
- Tricholemmoma
- Trichilemmal carcinoma
- Sebaceous adenoma
- Sebaceous carcinoma
- Adnexal clear cell carcinoma with comedonecrosis.

Nevomelanocytic

- Balloon cell nevus
- Balloon cell melanoma
- Clear cell melanoma
- Clear cell sarcoma.

Mesenchymal

- Clear cell dermatofibroma
- Clear cell atypical fibroxanthoma
- Clear cell fibrous papule
- Clear cell leiomyoma
- Dermal clear cell mesenchymal tumor
- Neurofibroma (focal)
- Hemangioblastoma
- Malignant glomus tumor.

Histiocytoses

- Papular xanthoma
- Xanthoma disseminatum
- Tuberous xanthoma
- Verruciform xanthoma
- Necrobiotic xanthogranuloma.

Salivary gland

- Acinic cell carcinoma
- Hyalinizing clear cell carcinoma
- Clear cell mucoepidermoid carcinoma.

Metastases

- Renal cell carcinoma
- Breast carcinoma
- Hepatocellular carcinoma
- Pulmonary adenocarcinoma and mesothelioma.

GRANULAR CELL TUMORS

- Granular cell tumor
- Congenital gingival granular cell tumor
- Primitive non-neural (polypoid) granular cell tumor
- Neurofibroma
- Perineurioma
- Neuroendocrine adenoma
- Dermatofibroma
- Epithelioid cell histiocytoma
- Dermatofibrosarcoma protuberans
- Atypical fibroxanthoma
- Fibrous papule
- Basal cell carcinoma
- Ameloblastoma
- Angiosarcoma
- Melanocytic tumors (compound nevus, melanoma)
- Myogenic tumors (leiomyoma, leiomyosarcoma)
- Hibernoma
- Adnexal tumors
- Paraganglioma.

PLEXIFORM TUMORS

Melanocytic

- Spitz nevus
- Spindle cell nevus
- Deep penetrating nevus
- Cellular blue nevus
- Congenital nevus
- Malignant melanoma, particularly spindle-cell variant
- Melanocytoneuroma.

Neural

- Neurofibroma
- Pigmented plexiform neurofibroma
- Neurilemmoma, including epithelioid variant
- Neurothekeoma
- Perineurioma
- Plexiform granular cell tumor.

Mesenchymal

- Dermatofibroma
- Atypical fibroxanthoma

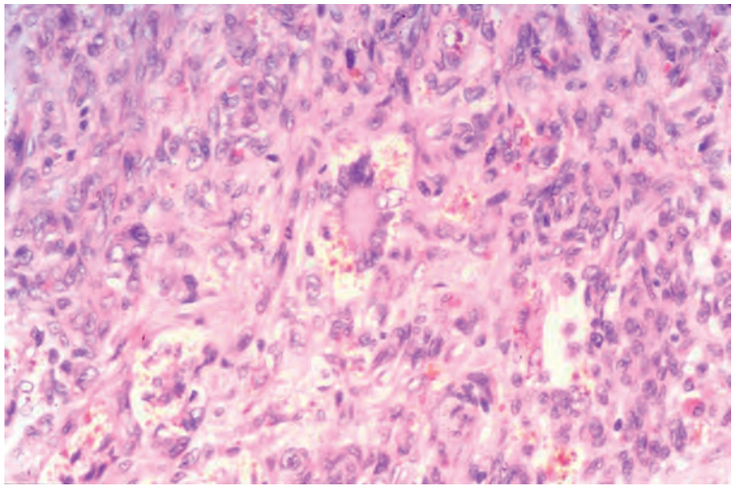


Figure 2.21 A Touton-like giant cell with hemosiderin-containing lipid layer in dermatofibroma. (H&E)

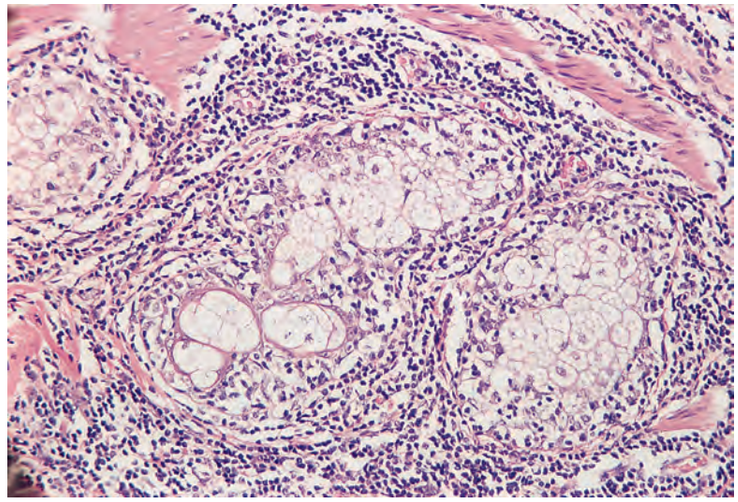


Figure 2.22 'Sebaceitis' in a case of herpes folliculitis. (H&E)

- Plexiform fibrohistiocytic tumor
- Fibrous hamartoma of infancy
- Leiomyoma (focal only)
- Ossifying plexiform tumor.

Miscellaneous

- Plexiform xanthoma
- Plexiform xanthomatous tumor.

TUMORS WITH HEMOSIDERIN (Fig. 2.21)

- Many vascular tumors (particularly Kaposi's sarcoma and angiosarcoma)
- Dermatofibroma (common)
- Dermatofibrosarcoma protuberans (rare)
- Atypical fibroxanthoma
- Giant cell tumor
- Melanoma
- Pleomorphic hyalinizing angiectatic tumor
- Hemosiderotic fibrohistiocytic lipomatous tumor
- Plexiform fibrohistiocytic tumor
- Epithelioid sarcoma
- Neurilemmoma.

Dermatofibromas, especially 'histiocytic', lipidized, and aneurysmal types, often contain a particular type of giant cell that resembles a Touton giant cell, with a central core of eosinophilic cytoplasm, multiple peripheral nuclei, and a surrounding lipid layer. These giant cells often have elongated or angulated contours. In addition, the nuclei appear to protrude into the lipid layer, in which hemosiderin granules are identified. This cell type is almost pathognomonic for dermatofibroma and can often help make the diagnosis even in a partial or poorly oriented biopsy specimen.

CLUES TO A PARTICULAR DISEASE

CLUES TO HERPES FOLLICULITIS (Fig. 2.22)

- Bottom-heavy infiltrate
- Sebaceitis
- Lichenoid changes around follicle ± epidermis
- Necrotic lower follicle
- Multinucleate epithelial cells, on searching.

CLUES TO GROVER'S DISEASE

- Focal acantholytic dyskeratosis with spongiosis
- Late lesions have elongated rete ridges and may resemble an early solar keratosis
- Eosinophils and less thick parakeratotic plugs may distinguish it from Darier's disease. The Darier variant may have a thick plug.

CLUES TO PITYRIASIS RUBRA PILARIS

- Most early cases are easily missed
- Alternating orthokeratosis and parakeratosis takes at least 14 days (probably longer) to develop
- Acantholytic dyskeratosis may be a clue; it is unfortunately uncommon (perhaps 1 in 20 biopsies).

CLUES TO CICATRICIAL PEMPHIGOID

- Subcutaneous blister with neutrophils
- Split may extend down follicles
- Dermal fibrosis (detected early by the presence of parallel collagen, on polarization)
- Extruded sebaceous gland within the blister.

Remember that even early lesions may show dermal fibrosis because blisters tend to recur at the site of a previous one.

CLUES TO EPIDERMOLYSIS BULLOSA ACQUISITA

- Antibodies deposit in the dermal floor in salt-split skin
- U-serrated immunodeposition pattern.

There are three patterns of linear fluorescence at the basement membrane zone: true linear, n-serrated, and u-serrated. The u-serrated pattern differentiates type VII targeting diseases (epidermolysis bullosa acquisita and bullous lupus erythematosus) from other subepidermal bullous autoimmune diseases (see p. 164).

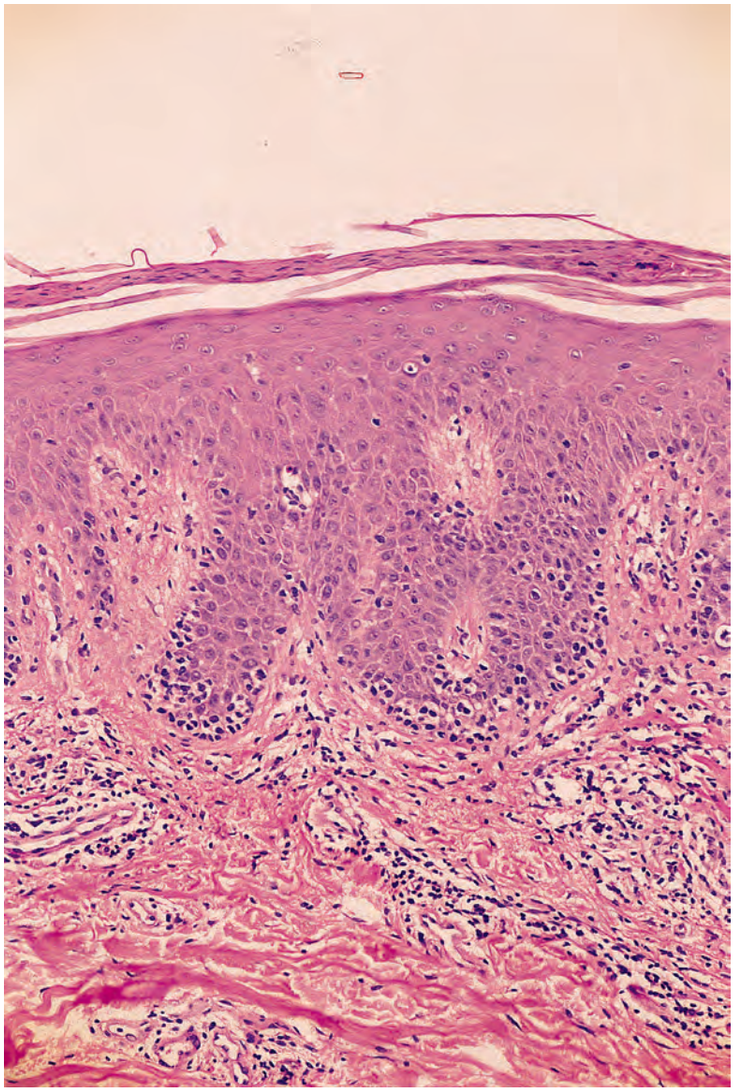


Figure 2.23 Mycosis fungoides. Note the epidermotropism and haloed lymphocytes within the epidermis. (H&E)

CLUES TO MYCOSIS FUNGOIDES (Fig. 2.23)

- Pautrier's microabscesses (only present in one-third)
- Haloed lymphocytes
- Epidermotropism without spongiosis
- Lymphocytes aligned within the basal layer
- Hyperconvoluted intraepidermal lymphocytes
- Epidermal lymphocytes larger than dermal ones
- Filling of the papillary dermis
- The 'bare underbelly' sign (unreliable)
- Fibrotic, thickened papillary dermis.

CLUES TO ALOPECIA AREATA

- Virtually all terminal follicles in the same stage
- 'Swarm of bees' (lymphocytes) in the hair bulb
- Increased catagen/telogen at advancing edge
- Presence of nanogen follicles.

CLUES TO ANDROGENETIC ALOPECIA

- Progressive decrease in follicular size
- Increase in vellus follicles
- Follicles do not extend into subcutis
- Increase in telogen hairs.

LATE BULLOUS LESIONS

Dermatitis herpetiformis:	Intracorneal nuclear dust aggregates
Pemphigus foliaceus:	Dyskeratotic cells with hyperchromatic nuclei in granular layer.

GRANULOMA ANNULARE VERSUS NECROBIOSIS LIPOIDICA

Necrobiosis lipoidica:	Likened to 'stacks of plates' with multilayered necrobiosis and 'open ends'; thickened collagen bundles may be seen within palisaded granulomas. Numerous plasma cells favor this diagnosis
Granuloma annulare:	Usually not multilayered and open ended, but palisading continues around the edges of the palisading granulomas; central acid mucopolysaccharides; plasma cells uncommon.

GRANULOMA ANNULARE VERSUS LICHEN NITIDUS

In disseminated granuloma annulare, small, poorly formed granulomas may develop in the upper dermis, sometimes mimicking lichen nitidus. Granuloma annulare does not usually have claw-like acanthotic downgrowths at the edge; it often has focal 'necrobiosis' (collagenolysis).

CLUES TO TRICHOEPITHELIOMA (OVER BCC)

- Papillary mesenchymal bodies ('stromal induction')
- $CD34^+$ stromal cells around the island
- No clefts around the nests
- Presence of $CD20^+$ Merkel cells
- Ruptured keratinous cysts
- Only basal layer *bcl*-2 expression
- A central dell/depression in the skin surface.

CLUE TO ANGIOSARCOMA

- A positive head-tilt maneuver.

If an angiosarcoma of the head or neck is present, placing the head below the level of the heart results in the area of involvement becoming more violaceous and engorged (see p. 1108).

CLUES TO KAPOSI'S SARCOMA

- Abnormal tissue spaces in the dermis
- Promontory sign (small vessel protruding into an abnormal space)
- Hemosiderin and plasma cells

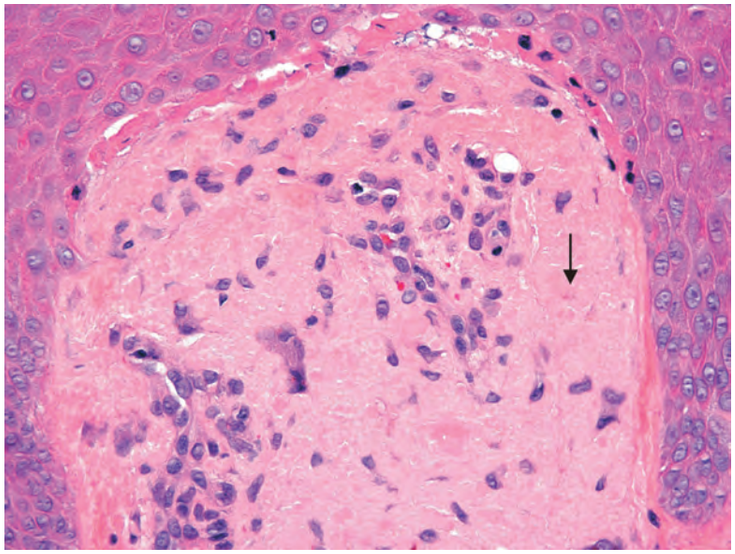


Figure 2.24 Cutaneous amyloidosis. Dendritic melanophages within hyaline deposits in the papillary dermis. (H&E)

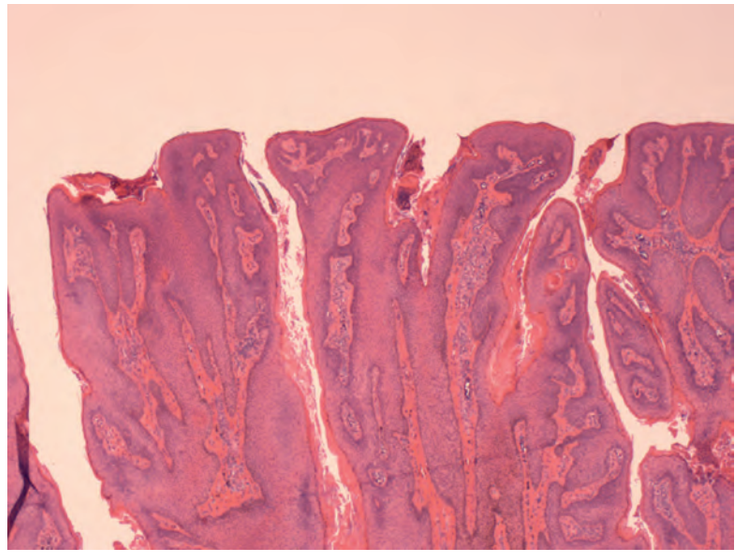


Figure 2.25 Epidermal nevus with flat-topped papillomatosis – the 'mesa' sign. (H&E)

- Stuffing of all dilated neoplastic vessels with erythrocytes in the absence of plasma
- Established lesions have the usually documented features.

CLUES TO BACILLARY ANGIOMATOSIS

Pyogenic granuloma-like lesion with nuclear dust and clumps of purplish material.

CLUES TO AMYLOIDOSIS (Fig. 2.24)

- Pale pink hyaline material in the papillary dermis
- Dendritic melanophages are present in some deposits. They are 'diagnostic'.

PARANEOPLASTIC DERMATOSES

In a useful review, Chung *et al*. (J Am Acad Dermatol 2006;54:745–762) listed 16 of the best-established paraneoplastic dermatoses that display distinctive clinical and pathological features. They are the following:

- Acanthosis nigricans
- Acquired ichthyosis
- Bazex's syndrome
- Cutaneous amyloidosis
- Dermatomyositis
- Erythema gyratum repens
- Hypertrichosis lanuginosa acquisita
- Leser–Trélat sign
- Multicentric reticulohistiocytosis
- Necrobiotic xanthogranuloma
- Necrolytic migratory erythema
- Paraneoplastic pemphigus
- Pyoderma gangrenosum
- Scleromyxedema
- Sweet's syndrome
- Tripe palms.

Granuloma annulare could also have been added.

CLUE TO EPIDERMAL NEVI – THE 'MESA' SIGN (Fig. 2.25)

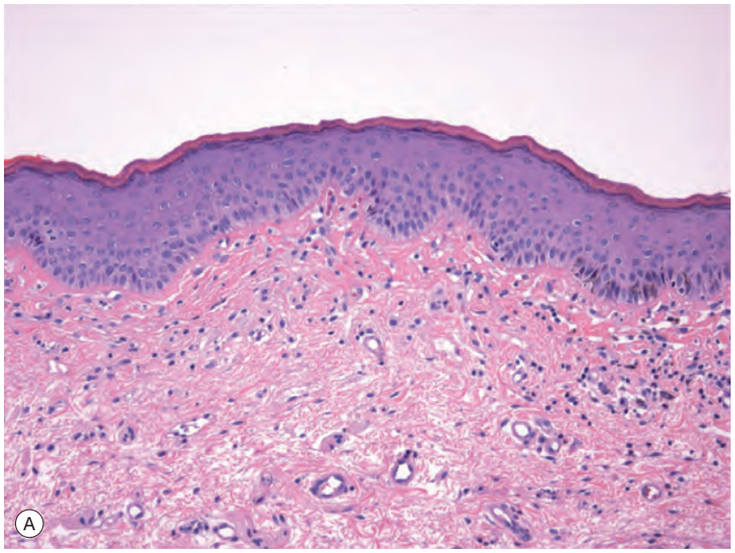
A helpful clue to the diagnosis of epidermal nevus is the 'mesa sign'. The tips of epidermal papillations are often flattened in epidermal nevi, resembling the flat-topped hill with steep sides that characterizes this geological formation. Papillomatous tips tend to be rounded or pointed in other, similar-appearing lesions, such as verrucae and seborrheic keratoses.

GENERAL HELPFUL HINTS AND CAUTIONS

NEARLY NORMAL SKIN (Fig. 2.26)

A number of cutaneous lesions, including some that may have striking clinical findings, show minimal discernible abnormalities in routine H&E-stained sections, especially at low magnification. These have also been called 'invisible dermatoses' or 'nothing lesions'. Diagnosis in such cases requires accurate clinical information, special staining for organisms or connective tissue changes, or occasionally ultrastructural study (e.g., in the case of depigmented or hypopigmented disorders). The following is a list of disorders that give the impression of nearly normal skin:

- Pityriasis alba
- Tinea versicolor
- Dermatophytosis
- Pitted keratolysis
- Urticaria
- Telangiectasia macularis eruptiva perstans
- Macular amyloidosis
- Solar elastosis
- Anetoderma



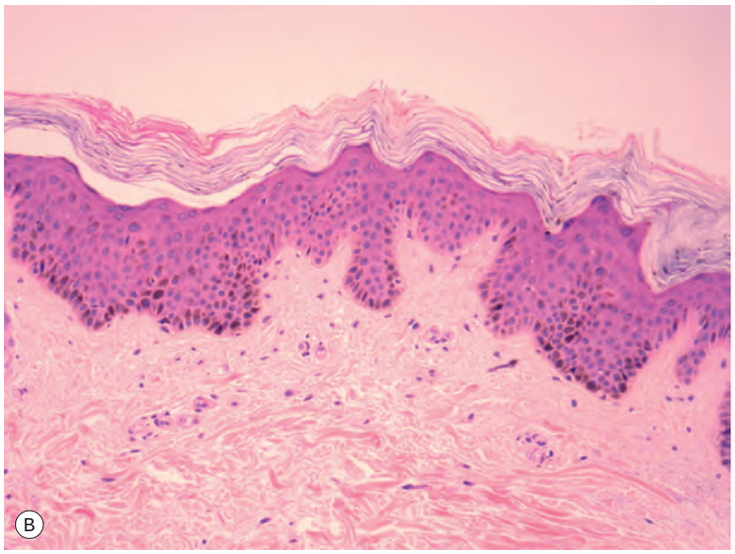


Figure 2.26 Nearly normal skin. These are examples of lesions in which histopathologic changes on H&E stained sections are minimal. **(A)** Vitiligo; **(B)** acquired ichthyosis. (H&E)

- Papillary and mid-dermal elastolysis
- Cutis laxa
- Connective tissue nevus
- Miliaria crystallina
- Hyperpigmented disorders
- Hypopigmented disorders
- Ichthyosis vulgaris, acquired ichthyosis
- Anhidrotic ectodermal dysplasia
- Dermal melanocytosis
- Nevus flammeus.

BEWARE OF KERATOACANTHOMA SIMULANTS

- Clinically, squamous cell carcinomas may grow quickly in the very elderly, simulating a keratoacanthoma. Squamous cell carcinoma may arise in a keratoacanthoma; this is very common in patients older than age 85 years

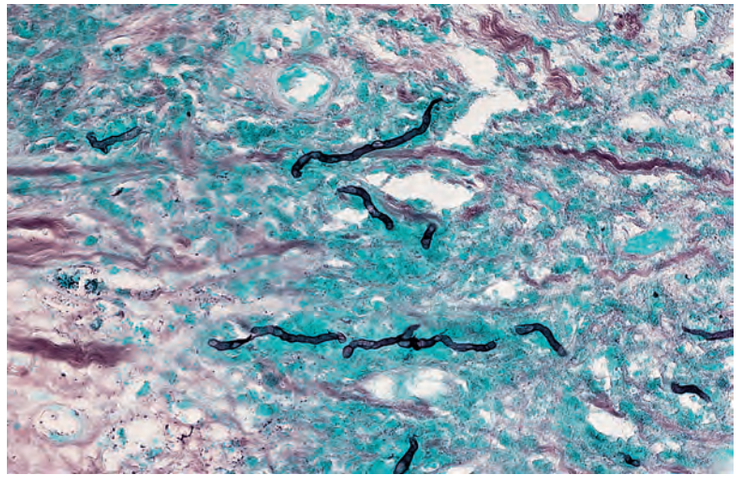


Figure 2.27 Equine fungus that is demonstrable only with silver stains. (Silver methenamine)

- Squamous cell carcinomas overlying rigid structures (e.g., cartilage of ear, base of nose, or bone of the tibia) may have infolding of margins simulating the architecture of a keratoacanthoma
- Keratoacanthomas have a unique pattern of cell differentiation (pink cytoplasm and large central cells).

BE CAUTIOUS WITH AMYLOID STAINS

- In solar elastotic skin, false-positive staining may occur with Congo red because differentiation may not remove all the stain from elastotic collagen
- A progressive stain (alkaline Congo red) may be better in these circumstances
- False-negative reactions may occur with the Congo red stain in macular amyloidosis
- The crystal violet stain is the most useful stain for amyloid keratin.

'UP IT HALF A GRADE'

The author still remembers the advice given to him by Malcolm B. Dockerty, MD, at the Mayo Clinic more than 35 years ago.

- If it is a lesion on the lip, 'up it half a grade'
- If it is a conjunctival nevus, 'down it half a grade'.

'DO SERIALS, NOT DEEPERS'

If suppurative granulomas are present, a fungal element (e.g., asteroid body in sporotrichosis) is usually present in each granuloma. Serial sections will ensure that the entire focus is sampled. Random deeper levels may miss the organism.

FUNGI MAY BE MISSED ON PAS STAIN (Fig. 2.27)

- 'Dead' fungi do not always stain with the PAS method
- The equine fungus *Phythium* does not stain.

The silver methenamine method will stain the fungi in both cases, but it is not always reliable with the zygomycoses.

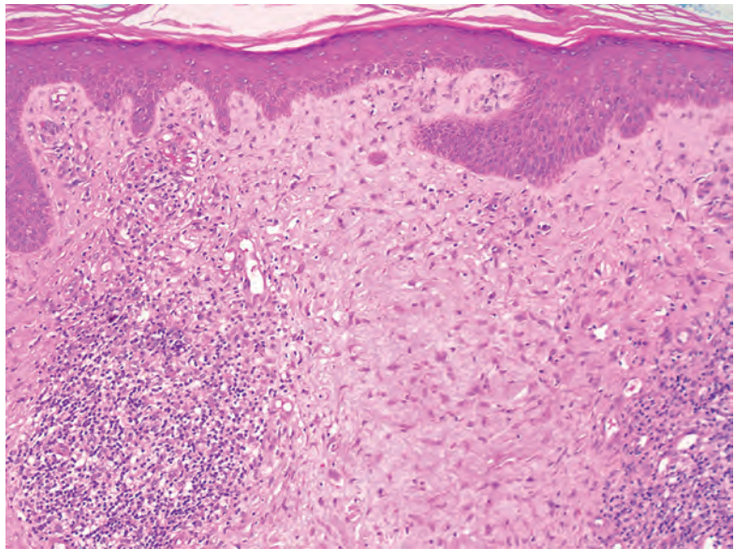


Figure 2.28 Pretibial pruritic papular dermatitis (PPPD). This neglected entity has a widened papillary dermis with stellate cells. It has a vague scanning power resemblance (apart from the expanded papillary dermis) to pigmented purpuric dermatosis (PPD). (H&E)

DERMAL NEUTROPHILS – OFTEN FORGOTTEN

Dermal and/or subcutaneous neutrophils may be seen in numerous conditions. They are discussed in Chapter 40. The author has temporarily 'missed' some of the following conditions through failure to think of them:

- Infections
- Acute cutis laxa
- α_1-Antitrypsin deficiency
- Eruptive xanthoma (extracellular lipid may assist)
- Folliculitis on deeper levels
- Excoriation on deeper levels
- Neutrophilic urticaria
- Erythema nodosum leprosum
- Dermatomyositis
- Polymorphic light eruption.

See Chapter 40 (Table 40.1) for a complete list.

ITCHING ANKLES (Fig. 2.28)

There are many causes of pruritus of the lower pretibial region, only some of which are listed here. The conditions listed include several that can be fully characterized by special stains or supporting clinical history:

- Lichen planus/hypertrophic lichen planus
- Lichen simplex chronicus
- Lichen amyloidosus
- Arthropod bites
- Itching purpura
- Pretibial pruritic papular dermatitis (see p. 96).

Clinically, pretibial pruritic papular dermatitis resembles lichen simplex chronicus or lichen amyloidosus; pathologically, it resembles pigmented purpuric dermatosis but with more papillary dermal fibrosis and no hemosiderin. In other words, 'triple P-D resembles double P-D'.

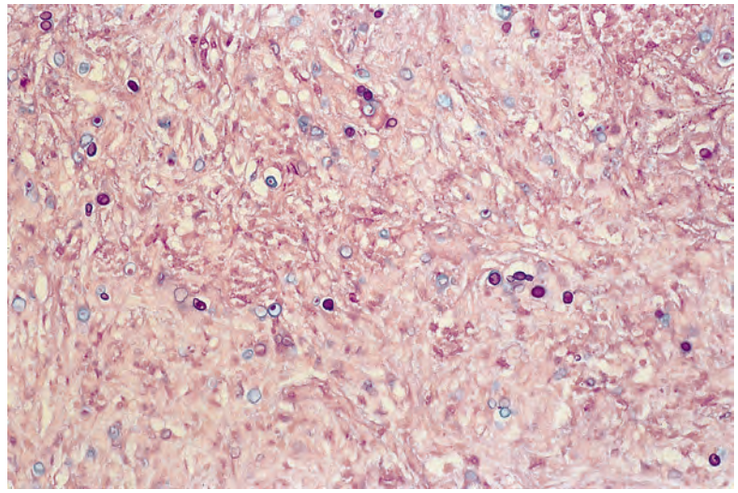


Figure 2.29 Cryptococcus. The capsule stains light blue and the cell wall a reddish color. (Alcian blue–PAS)

THE DEMONSTRATION OF CRYPTOCOCCI (Fig. 2.29)

- Cryptococci are doubly refractile
- They are mucicarmine positive
- On Alcian blue–PAS, a beautiful contrast is seen between cell wall and capsule
- It does not stain with Congo red.

THE EDGE OF BOWEN'S DISEASE

Pagetoid cells are often present at the edge of Bowen's disease. They may simulate melanoma or Paget's disease in small (2 or 3 mm) punch biopsies.

FALSE-NEGATIVE IMMUNOPEROXIDASE

The use of microwaves for fixation may release excess antigens leading to the prozone phenomenon. A false-negative results, although some staining may occur at the periphery of the tumor. The dilution of the antisera used must be changed in these circumstances. Automated staining is another cause.

MISCELLANEOUS HINTS

- Psoriasis is a 'mitotic disease'. Look for mitoses in basal keratinocytes
- In hypertrophic lichen planus, the lichenoid activity may be confined to the tips of the rete pegs
- Early lichen sclerosus et atrophicus may have lichenoid histological features
- Acantholytic solar keratoses often mimic basal cell carcinoma clinically; they may be resistant to cryotherapy.

The lichenoid reaction pattern ('interface dermatitis')

3

INTRODUCTION

The lichenoid reaction pattern (lichenoid tissue reaction, interface dermatitis) is characterized histologically by epidermal basal cell damage.[1–3] This takes the form of cell death and/or vacuolar change (liquefaction degeneration). The cell death usually involves only scattered cells in the basal layer that become shrunken with eosinophilic cytoplasm. These cells, which have been called Civatte bodies, often contain pyknotic nuclear remnants. Sometimes, fine focusing up and down will reveal smaller cell fragments, often without nuclear remnants, adjacent to the more obvious Civatte bodies.[4] These smaller fragments have separated from the larger bodies during the process of cell death. Ultrastructural studies have shown that the basal cells in the lichenoid reaction pattern usually die by apoptosis, a comparatively recently described form of cell death, which is quite distinct morphologically from necrosis.[5,6]

Before discussing the features of apoptosis, mention will be made of the term '**interface dermatitis**', which is widely used. It has been defined as a dermatosis in which the infiltrate (usually composed mostly of lymphocytes) appears "to obscure the junction when sections are observed at scanning magnification."[7] The term is not used uniformly or consistently. Some apply it to most dermatoses with the lichenoid tissue reaction. Others use it for the subgroup in which the infiltrate truly obscures the interface (erythema multiforme, fixed drug eruption, paraneoplastic pemphigus, some cases of subacute lupus erythematosus and pityriasis lichenoides). The infiltrate may obscure the interface in lymphomatoid papulosis, but basal cell damage is not invariable. Many apply the term, also, to lichen planus and variants, in which the infiltrate characteristically 'hugs' the basal layer without much extension into the epidermis beyond the basal layer. Crowson *et al*. have expanded the concept of interface dermatitis to include neutrophilic and lymphohistiocytic forms, in addition to the traditional lymphocytic type. They also subdivide the lymphocytic type into a cell-poor type and a cell-rich type.[8] Erythema multiforme, which they list as a cell-poor variant, is sometimes quite 'cell rich'. The author prefers the traditional term 'lichenoid' for this group of dermatoses because it is applicable more consistently than interface dermatitis and it is less likely to be applied as a 'final sign-out diagnosis', which is often the case with the term interface dermatitis. The term is so entrenched that it is unlikely to disappear from the lexicon of dermatopathology.

In *apoptosis*, single cells become condensed and then fragment into small bodies by an active budding process (**Fig. 3.1**). In the skin, these condensed apoptotic bodies are known as Civatte bodies (discussed previously). The smaller apoptotic bodies, some of which are beyond the resolution of the light microscope, are usually phagocytosed quickly by adjacent parenchymal cells or by tissue macrophages.[5] Cell membranes and organelles remain intact for some time in apoptosis, in contradistinction to necrosis where breakdown of these structures is an integral and prominent part of the process. Keratinocytes contain tonofilaments that act as a 'straitjacket' within the cell, and therefore budding and fragmentation are less complete in the skin than they are in other cells in the body undergoing death by apoptosis. This is particularly so if the keratinocyte has accumulated filaments in its cytoplasm, as occurs with its progressive maturation in the epidermis. The term 'dyskeratotic cell' is usually used for these degenerate keratinocytes. The apoptotic bodies that are rich in tonofilaments are usually larger than the others; they tend to 'resist' phagocytosis by parenchymal cells, although some are phagocytosed by macrophages. Others are extruded into the papillary dermis, where they are known as *colloid bodies*. These bodies appear to trap immunoglobulins nonspecifically, particularly the IgM molecule, which is larger than the others. Apoptotic cells can be labeled by the TUNEL (terminal transferase-mediated dUTP nick end labeling) reaction.[9]

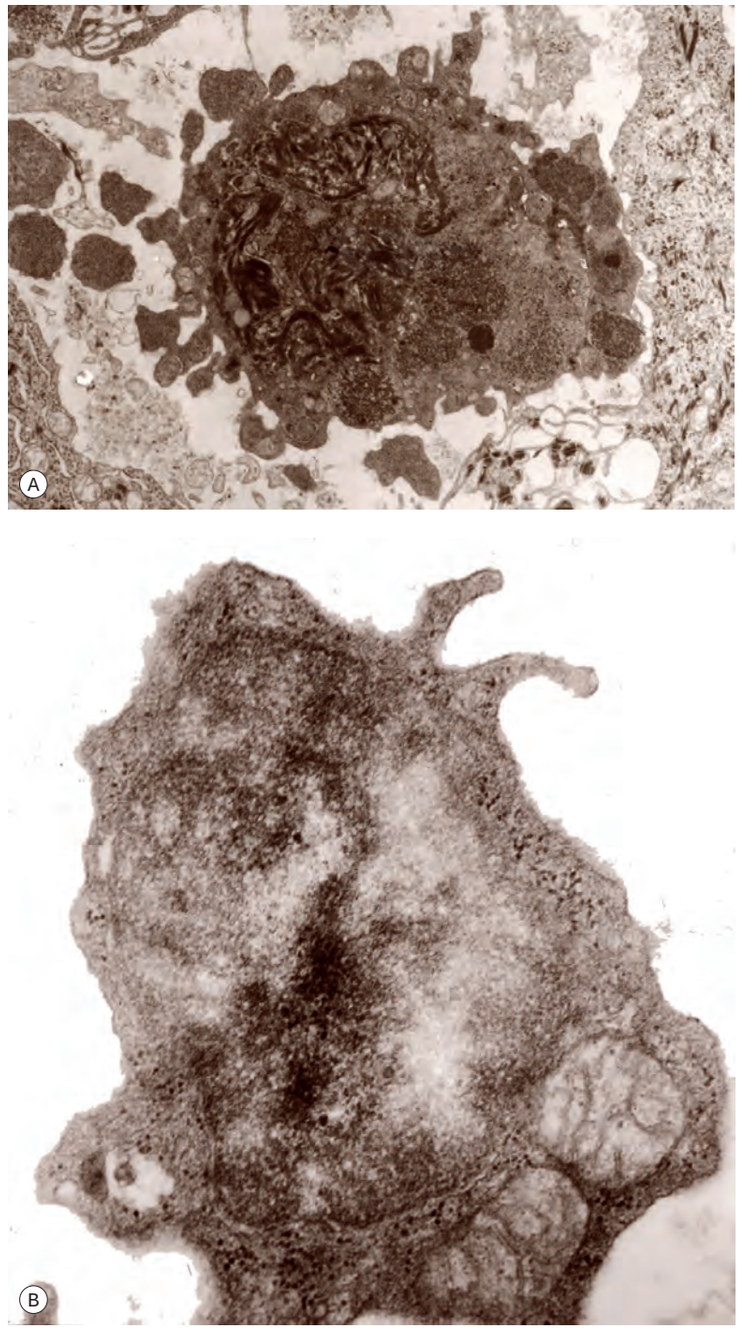


Figure 3.1 (A) Apoptosis of a basal keratinocyte in lichen planus. There is surface budding and some redistribution of organelles within the cytoplasm. (Electron micrograph ×12,000) **(B) A tiny budding fragment in which the mitochondria have intact cristae.** (×25,000)

Some of the diseases included within the lichenoid reaction pattern show necrosis of the epidermis rather than apoptosis; in others, the cells have accumulated so many cytoplasmic filaments prior to death that the actual mechanism – apoptosis or necrosis – cannot be discerned by light or electron microscopy. The term 'filamentous degeneration' has been suggested for these cells;[10] on light microscopy, they are referred to as 'dyskeratotic cells' (discussed previously). Some dermatopathologists use the term 'necrotic keratinocyte' for these cells and also for keratinocytes that are obviously apoptotic. Note that apoptotic keratinocytes have been seen in normal skin, indicating that cell deletion also occurs as a normal physiological phenomenon.[11–13] As

Afford and Randhawa eloquently stated, "Apoptosis is the genetically regulated form of cell death that permits the safe disposal of cells at the point in time when they have fulfilled their intended biological function."[14] It also plays a role in the elimination of the inflammatory infiltrate at the end stages of wound healing.[15]

Although it is beyond the scope of this book, readers interested in apoptosis and the intricate mechanisms of its control should read the excellent studies published on this topic.[16–24] The various 'death receptors', essential effectors of any programmed cell death, were reviewed in 2003.[25] An important member of this group is tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which preferentially induces apoptosis in transformed but not normal cells. It is expressed in normal skin and cutaneous inflammatory diseases.[26] Another cell component that plays a role in apoptosis is the mitochondrion. This topic was reviewed in 2006.[27]

Ackerman has continued to present a minority view that apoptosis is a type of necrosis.[28] In reality, each is a distinctive form of cell death.

Vacuolar change (liquefaction degeneration) is often an integral part of the basal damage in the lichenoid reaction. Sometimes it is more prominent than the cell death. It results from intracellular vacuole formation and edema, as well as from separation of the lamina densa from the plasma membrane of the basal cells. Vacuolar change is usually prominent in lupus erythematosus, particularly the acute systemic form, and in dermatomyositis and some drug reactions.

As a consequence of the basal cell damage, there is variable *melanin incontinence* resulting from interference with melanin transfer from melanocytes to keratinocytes, as well as from the death of cells in the basal layer.[1] Melanin incontinence is particularly prominent in some drug-induced and solar-related lichenoid lesions, as well as in patients with marked racial pigmentation.

Another feature of the lichenoid reaction pattern is a variable *inflammatory cell infiltrate*. This varies in composition, density, and distribution according to the disease. An assessment of these characteristics is important in distinguishing the various lichenoid dermatoses. Because apoptosis, unlike necrosis, does not itself evoke an inflammatory response, it can be surmised that the infiltrate in those diseases with prominent apoptosis is of pathogenetic significance and not a secondary event.[5] Furthermore, apoptosis is the usual method of cell death resulting from cell-mediated mechanisms, whereas necrosis and possibly vacuolar change result from humoral factors, including the deposition of immune complexes.

One study has given some insight into the possible mechanisms involved in the variability of expression of the lichenoid tissue reaction in several of the diseases within this group. The study examined the patterns of expression of the intercellular adhesion molecule-1 (ICAM-1).[29] Keratinocytes in normal epidermis have a low constitutive expression of ICAM-1, rendering the normal epidermis resistant to interaction with leukocytes. Therefore, induction of ICAM-1 expression may be an important factor in the induction of leukocyte-dependent damage to keratinocytes.[29] In lichen planus, ICAM-1 expression is limited to basal keratinocytes, whereas in subacute cutaneous lupus erythematosus there is diffuse epidermal ICAM-1 expression, sometimes with basal accentuation. This pattern is induced by ultraviolet radiation and possibly mediated by tumor necrosis factor-α (TNF-α). In erythema multiforme, there is strong basal expression of ICAM-1, with cell surface accentuation and similar pockets of suprabasal expression, probably induced by herpes simplex virus infection.[29]

Other molecules appear to play important roles in lichenoid dermatitis. IKKB, a subunit of the IκB kinase complex, is required for activation of NF-κB, a protein that controls DNA transcription. In an animal model, overexpression of IKKβ results in chronic inflammation with macrophages and $CD45^+$ cells, interface dermatitis, and increased production of inflammatory cytokines by keratinocytes. This process apparently occurs independently of T and B lymphocytes.[30] The type 1 interferon (IFN) system plays an important role in the interface dermatitis associated with autoimmune diseases, mediating a cytotoxic attack on basal keratinocytes. Evidence for this is the finding of IFN-inducible chemokine CXCL10 expression in the same location where $CXCR3^+$ cytotoxic lymphocytes invade the epidermal basilar layer.[31] Using a model of reconstructed human epidermis, Farley *et al*. explored the important roles of the Fas ligand (the expression of which by donor T cells may be essential for cutaneous acute graft-versus-host reaction) and IFN-γ. These investigators found that cytoid body formation and epidermal expression of ICAM-1 could be attributed to IFN-γ, whereas hypergranulosis was triggered by the Fas ligand, and vacuolar degeneration of the basilar layer appeared to be triggered by both the Fas ligand and IFN-γ.[32]

In summary, the lichenoid reaction pattern includes a heterogeneous group of diseases that have in common basal cell damage.[33] The histogenesis is also diverse and includes cell-mediated and humoral immune reactions and possibly ischemia in one condition. A discussion of the mechanisms involved in producing apoptosis is included in several of the diseases that follow. Scattered apoptotic keratinocytes can also be seen in the sunburn reaction in response to ultraviolet radiation;[34,35] these cells are known as 'sunburn cells'.[36] A specific histological diagnosis can usually be made by attention to such factors as:

- the nature and extent of the basal damage;
- the nature, composition, and distribution of the inflammatory reaction;
- the amount of melanin incontinence that results from the basal damage;
- the coexistence of another tissue reaction;[37] and;
- other individual characteristics.[2]

These points are considered further in **Tables 3.1–3.3**.

A discussion of the various lichenoid (interface) dermatoses follows. The conditions listed as 'other lichenoid (interface) diseases' are discussed only briefly because they are considered in detail in other chapters.

LICHENOID (INTERFACE) DERMATOSES

LICHEN PLANUS

Lichen planus, a relatively common eruption of unknown etiology, displays violaceous, flat-topped papules, which are usually pruritic.[38,39] A network of fine white lines (Wickham's striae) may be seen on the surface of the papules. There is a predilection for the flexor surface of the wrists, the trunk, the thighs, and the genitalia. Palmoplantar lichen planus appears to be more common than once thought.[40,41] It is one of the most disabling, painful, and therapy-resistant variants of lichen planus.[42] Oral lesions are common; rarely, the esophagus is also involved.[43,44] Lesions localized to the lip,[45] vulva,[46,47] and an eyelid[48] have been reported. Lichen planus localized to a radiation field may represent an isomorphic response.[49,50] It has also developed in a healed herpes zoster scar.[51] Nail changes occur[52–55] and, as with oral lesions, these may be the only manifestations of the disease.[56,57] Clinical variants include atrophic, annular, hypertrophic, linear, zosteriform,[58–60] erosive, oral, actinic, follicular, erythematous, and bullous forms. They are discussed further later. An eruptive variant also occurs.[61] Spontaneous resolution of lichen planus is usual within 12 months, although postinflammatory pigmentation may persist for some time afterwards.[62]

Familial cases are uncommon, and rarely these are associated with HLA-D7.[63–66] An association with HLA-DR1 has been found in non-familial cases.[67] There is an increased frequency of HLA-DR6 in Italian patients with hepatitis C virus-associated oral lichen planus.[68] Lichen planus is rare in children,[69–76] but some large series have been

Table 3.1 Key histopathological features of various lichenoid diseases

Disease	Histopathological features
Lichen planus	Prominent Civatte bodies, band-like inflammatory infiltrate, wedge-shaped hypergranulosis. Hypertrophic form has changes limited to the tips of the acanthotic downgrowths and often superadded lichen simplex chronicus. The infiltrate extends around hair follicles in lichen planopilaris. Pigment incontinence is conspicuous in erythema dyschromicum perstans.
Lichen nitidus	Focal (papular) lichenoid lesions; some giant cells; dermal infiltrate often 'clasped' by acanthotic downgrowths.
Lichen striatus	Clinically linear; irregular and discontinuous lichenoid reaction; infiltrate sometimes around follicles and sweat glands.
Lichen planus-like keratosis	Solitary; prominent Civatte body formation; solar lentigo often at margins.
Lichenoid drug eruptions	Focal parakeratosis; eosinophils, plasma cells and melanin incontinence may be features. Deep extension of the infiltrate occurs in photolichenoid lesions.
Fixed drug eruptions	Interface-obscuring infiltrate, often extends deeper than erythema multiforme; cell death often above basal layer; neutrophils often present.
Erythema multiforme	Interface-obscuring infiltrate; sometimes subepidermal vesiculation and variable epidermal cell death.
Graft-versus-host disease	Basal vacuolation; scattered apoptotic keratinocytes, sometimes with attached lymphocytes ('satellite cell necrosis'); variable lymphocytic infiltrate.
Lupus erythematosus	Mixed vacuolar change and Civatte bodies. SLE has prominent vacuolar change and minimal cell death. Discoid lupus away from the face has more cell death and superficial and deep infiltrate; mucin; follicular plugging; basement membrane thickening. Some cases resemble erythema multiforme with cell death at all layers.
Dermatomyositis	May resemble acute lupus with vacuolar change, epidermal atrophy, some dermal mucin; infiltrate usually superficial and often sparse.
Poikilodermas	Vacuolar change; telangiectasia; pigment incontinence; late dermal sclerosis.
Pityriasis lichenoides	Acute form combines lymphocytic vasculitis with epidermal cell death; interface-obscuring infiltrate; focal hemorrhage; focal parakeratosis.
Paraneoplastic pemphigus	Erythema multiforme-like changes with suprabasal acantholysis and clefting; subepidermal clefting sometimes present.

Table 3.2 Diagnoses associated with various pathological changes in the lichenoid reaction pattern

Pathological change	Possible diagnoses
Vacuolar change	Lupus erythematosus, dermatomyositis, drugs and poikiloderma
Interface-obscuring infiltrate	Erythema multiforme, fixed drug eruption, pityriasis lichenoides (acute), paraneoplastic pemphigus, lupus erythematosus (some)
Purpura	Lichenoid purpura
Cornoid lamella	Porokeratosis
Deep dermal infiltrate	Lupus erythematosus, syphilis, drugs, photolichenoid eruption
'Satellite cell necrosis'	Graft-versus-host disease, eruption of lymphocyte recovery, erythema multiforme, paraneoplastic pemphigus, regressing plane warts, drug reactions
High apoptosis	Phototoxic reactions, adult-onset Still's disease, acrokeratosis paraneoplastica
Prominent pigment incontinence	Poikiloderma, drugs, 'racial pigmentation' and an associated lichenoid reaction, erythema dyschromicum perstans and related entities
Eccrine duct involvement	Erythema multiforme (drug induced), lichen striatus, keratosis lichenoides chronica, periflexural exanthem of childhood

Table 3.3 Diseases with the lichenoid and one or more coexisting tissue reaction patterns

Additional pattern	Possible diagnoses
Spongiotic	Drug reactions (see spongiotic drug reactions), lichenoid contact dermatitis, lichen striatus, late-stage pityriasis rosea, superantigen 'id' reactions
Granulomatous	Lichen nitidus, lichen striatus (rare), lichenoid sarcoidosis, hepatobiliary disease, endocrinopathies, infective reactions including secondary syphilis, herpes zoster infection, HIV infection, tinea capitis, *Mycobacterium marinum*, and *M. haemophilum*; drug reactions (often in setting of Crohn's disease or rheumatoid arthritis – atenolol, allopurinol, captopril, cimetidine, enalapril, hydroxychloroquine, simvastatin, sulfa drugs, tetracycline, diclofenac, erythropoietin)
Vasculitic	Pityriasis lichenoides, perniosis (some cases), pigmented purpuric dermatosis (lichenoid variant), persistent viral reactions, including herpes simplex
Vasculitic/spongiotic	Gianotti–Crosti syndrome, some other viral/putative viral diseases, rare drug reactions

published.[77–79] Lichen planus has been reported in association with immunodeficiency states,[80] internal malignancy,[81,82] including thymoma,[83] Still's disease,[84] primary biliary cirrhosis,[85,86] hypothyroidism,[87] peptic ulcer (but not *Helicobacter pylori* infection),[88] chronic hepatitis C infection,[89–99] hepatitis B vaccination,[100–109] influenza vaccination,[110] herpesvirus type 7 (HHV-7) replication,[111] simultaneous measles–mumps–rubella and diphtheria–tetanus–pertussis-polio vaccinations,[112] stress,[113] vitiligo,[114] pemphigus,[115] porphyria cutanea tarda,[116] radiotherapy,[117] ulcerative colitis,[118] chronic giardiasis,[119] a Becker's nevus,[120] and lichen sclerosus et atrophicus with coexisting morphea.[121] Despite the association between lichen planus and hepatitis C (HCV) infection, its incidence in patients with lichen planus in some areas of the world is not increased compared with that of a control group.[122,123] Lichen planus patients have a significantly higher risk than controls of being HCV seropositive, and there is a similar odds ratio of having lichen planus among HCV patients; this appears to only partly depend on geographic effect.[124] A large European study showed that lichen planus is associated with HCV but not with HBV.[125] On the other hand, although HCV and oral lichen planus are significantly associated in a number of studies, most patients with oral lichen planus are not affected by HCV.[126] The exacerbation or appearance of lichen planus during the treatment of HCV infection and other diseases with IFN-α has been reported.[127] Furthermore, effective therapy for the HCV does not clear the lichen planus.[128] Reports linking lichen planus to infection with human papillomavirus may be a false-positive result.[129,130]

Squamous cell carcinoma is a rare complication of the oral and vulval cases of lichen planus and of the hypertrophic and ulcerative variants (see later).[131–135] One study found no significant transformation risk of cutaneous lichen planus to squamous cell carcinoma, although there is a significant risk of malignant transformation in mucosal lichen planus.[136] A contact allergy to metals, flavorings, and plastics may be important in the etiology of oral lichen planus.[137] The role of mercury in dental amalgams is discussed further later.

Cell-mediated immune reactions appear to be important in the pathogenesis of lichen planus.[138] It has been suggested that these reactions are precipitated by an alteration in the antigenicity of epidermal keratinocytes, possibly caused by a virus or a drug or by an allogeneic cell.[139] Keratinocytes in lichen planus express HLA-DR on their surface, and this may be one of the antigens that has an inductive or perpetuating role in the process.[140–142] Keratinocytes also express fetal cytokeratins (CK13 and CK8/18), but whether they are responsible for triggering the T-cell response is speculative.[143] The cellular response initially consists of $CD4^+$ lymphocytes;[144] they are also increased in the peripheral blood.[145] In recent years, attention has focused on the role of cytotoxic $CD8^+$ lymphocytes in a number of cell-mediated immune reactions in the skin. They appear to play a significant role as the effector cell, whereas the $CD4^+$ lymphocyte, usually present in greater numbers,[146] plays its traditional 'helper' role. In lichen planus, $CD8^+$ cells appear to recognize an antigen associated with MHC class I on lesional keratinocytes, resulting in their death by apoptosis.[147] *Bcl*-2, a proto-oncogene that protects cells from apoptosis, is increased in lichen planus.[148] It may allow some cells to escape apoptosis, prolonging the inflammatory process.[148] The recruitment of lymphocytes to the interface region may be the result of the chemokine MIG (monokine induced by IFN-γ).[149] Lymphokines produced by these T lymphocytes – including IFN-γ, interleukins (IL)-1β, -4 and -6, perforin,[150] granzyme B,[151] granulysin,[152] T-cell-restricted intracellular antigen (Tia-1), and tumor necrosis factor – may have an effector role in producing the apoptosis of keratinocytes.[153,154] The other pathway involves the binding of Fas ligand to Fas, which triggers a caspase cascade.[155,156] In both oral and cutaneous lichen planus, $CD8^+$ cells predominate in the epithelial and subepithelial compartments, with $CD4^+$ cells playing a helper role by secretion of Th1 cytokines. Activated $CD8^+$ cells promote basilar keratinocyte apoptosis through either granzyme B or Fas/Fas ligand pathways.[157] As one possible explanation of how this mechanism might work in lichen planus, elevated osteopontin levels may upregulate CD44, with resultant T-cell resistance to apoptosis and accumulation of activated T cells in lichen planus lesions.[158] Gene expression profiling in lichen planus has found that type I IFN inducible genes are significantly expressed.[159] Plasmacytoid dendritic cells appear to be a major source of these type I IFNs in lichen planus. They play a major role in cytotoxic skin inflammation by increasing the expression of IPIO/CXCRIO and recruiting effector cells via CXCR3.[160] The CXCR3 ligand, CXCL9, is the most significant marker for lichen planus.[159] A unique subclass of cytotoxic T lymphocyte (γδ) is also found in established lesions.[161] Langerhans cells are increased, and it has been suggested that these cells initially process the foreign antigen.[141] Factor XIIIa-positive cells and macrophages expressing lysozyme are found in the dermis.[144]

There is evidence that expression of the microRNAs, miRNA-146a and miRNA-155, is increased in lesions of oral lichen planus. MicroRNAs are known to participate in immune response regulation.[162]

Increased oxidative stress, increased lipid peroxidation, and an imbalance in the antioxidant defense system are present, but their exact role in the pathogenesis of lichen planus is unknown.[163]

Matrix metalloproteinases may play a concurrent role by destroying the basement membrane.[164] Evidence from an animal model suggests that keratinocytes require cell survival signals, derived from the basement membrane, to prevent the onset of apoptosis.[165] In oral lichen planus, MMP-1 and MMP-3 may be principally associated with erosion development.[166] Altered levels of heat shock proteins are found in the epidermis in lichen planus.[167]

Most studies have found no autoantibodies and no alteration in serum immunoglobulins in lichen planus.[168] However, a lichen planus-specific antigen has been detected in the epidermis, and a circulating antibody to it has been found in the serum of individuals with lichen planus.[169,170] Its pathogenetic significance remains uncertain. Antibodies to desmoplakins I and II have been found in oral and genital lesions, possibly representing epitope spreading.[171]

Replacement of the damaged basal cells is achieved by an increase in actively dividing keratinocytes in both the epidermis and the skin appendages. This is reflected in the pattern of keratin expression, which resembles that seen in wound healing; cytokeratin 17 (CK17) is found in suprabasal keratinocytes.[172]

Treatment of lichen planus

Potent topical corticosteroids remain the treatment of choice for lichen planus in patients with classic and localized disease. For widespread disease and mucosal lesions, a short course of systemic corticosteroids may provide some relief.[173] Cyclosporine (ciclosporin), hydroxychloroquine, retinoids, dapsone, mycophenolate mofetil,[174] sulfasalazine,[175] alefacept,[176] and efalizumab[177] have all been used at various times. Mycophenolate mofetil has been shown to be effective in severe ulcerative lichen planus.[178] Erosive oral disease has been treated with tacrolimus mouthwash,[179] whereas erosive flexural lichen planus has responded to thalidomide and 0.1% tacrolimus ointment.[180] Palmoplantar disease may be resistant to treatment and require cyclosporine.[41]

Histopathology[181]

The basal cell damage in lichen planus takes the form of multiple, scattered Civatte bodies (**Fig. 3.2**). Eosinophilic colloid bodies, which are PAS positive and diastase resistant, are found in the papillary dermis (**Fig. 3.3**). They measure approximately 20 μm in diameter. The basal damage is associated with a band-like infiltrate of lymphocytes and some macrophages that press against the undersurface of the epidermis (**Fig. 3.4**). Occasional lymphocytes extend into the basal layer, where they may be found in close contact with basal cells and sometimes with Civatte bodies. The infiltrate tends to obscure the interface but does not extend into the mid-epidermis. Karyorrhexis is sometimes seen in the dermal infiltrate.[182] Rarely, plasma cells can be found in cutaneous lesions,[183–186] but most often they are not identified – a feature that can be useful in differential diagnosis. In exceptional cases, they can be numerous.[184–186] In some instances, plasma cells may be found because cutaneous lesions have arisen in anatomic sites where these cells tend to be prevalent, such as the face, posterior neck, intertriginous sites, and pretibial areas. Although they are usually present in lesions adjacent to or on mucous membranes, plasma cells are sometimes surprisingly sparse even in these locations. There is variable melanin incontinence, but this is most conspicuous in lesions of long duration and in dark-skinned people.

Other characteristic epidermal changes include hyperkeratosis, wedge-shaped areas of hypergranulosis related to the acrosyringia and acrotrichia, and variable acanthosis. At times, the rete ridges become pointed, imparting a 'sawtooth' appearance to the lower epidermis. There is sometimes mild hypereosinophilia of keratinocytes in the malpighian layer. Small clefts (Caspary–Joseph spaces)[187] may form at the dermoepidermal junction secondary to the basal damage. The eccrine duct adjacent to the acrosyringium is sometimes involved.[188,189] A variant in which the lichenoid changes were localized entirely to the acrosyringium has been reported.[190] Transepidermal elimination with perforation is another rare finding.[191] The formation of milia may be a late complication.[192]

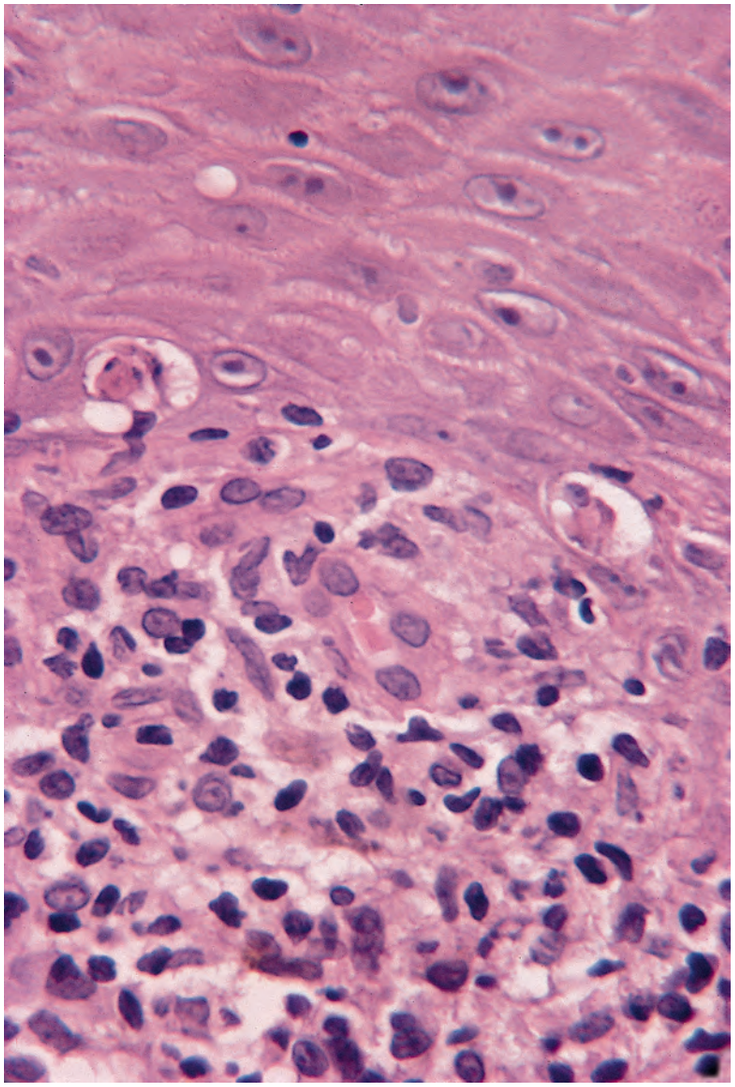


Figure 3.2 Lichen planus. Two apoptotic keratinocytes (Civatte bodies) are present in the basal layer of the epidermis. An infiltrate of lymphocytes touches the undersurface of the epidermis. (H&E)

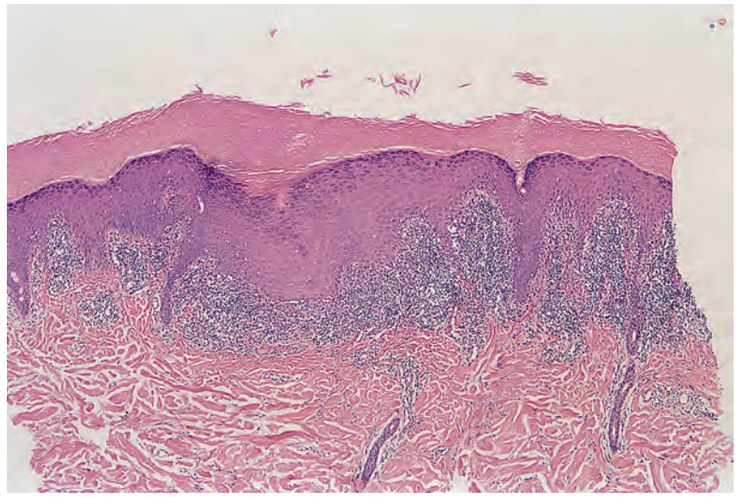


Figure 3.4 Lichen planus. A band-like infiltrate of lymphocytes fills the papillary dermis and touches the undersurface of the epidermis. (H&E)

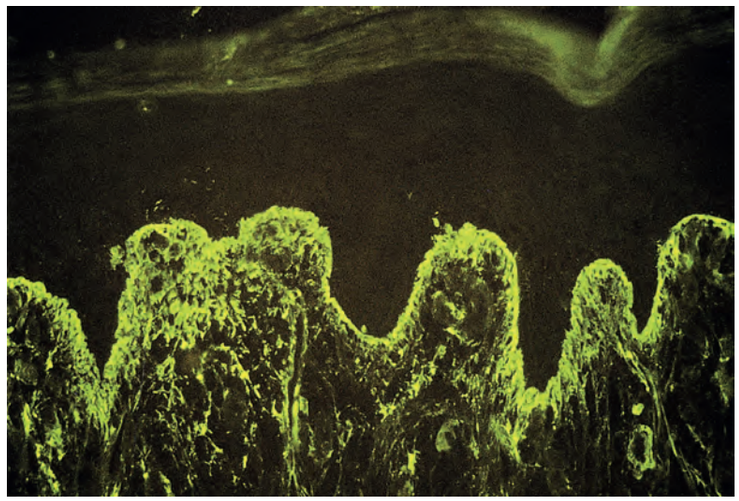


Figure 3.5 Lichen planus. A band of fibrin involves the basement membrane zone and extends into the papillary dermis. (Direct immunofluorescence)

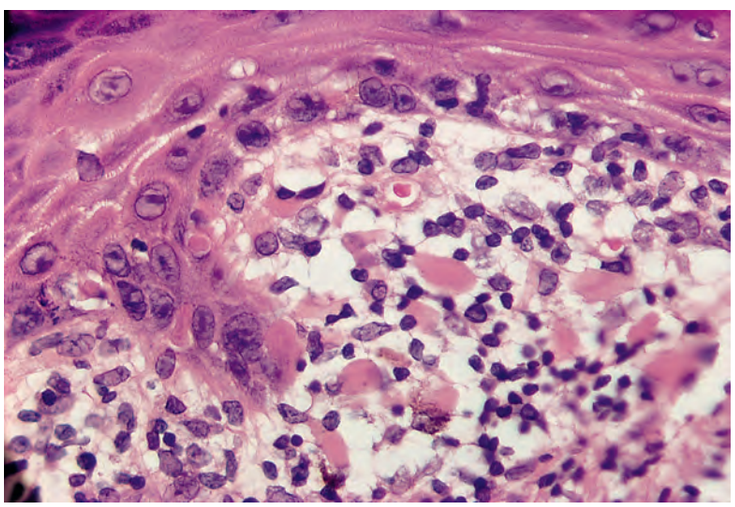


Figure 3.3 Lichen planus. There are numerous colloid bodies in the papillary dermis. (H&E)

Ragaz and Ackerman studied the evolution of lesions in lichen planus.[181] They found an increased number of Langerhans cells in the epidermis in the very earliest lesions, before there was any significant infiltrate of inflammatory cells in the dermis. In resolving lesions, the infiltrate is less dense, and there may be minimal extension of the inflammatory infiltrate into the reticular dermis.

As previously mentioned, some diseases exhibiting the lichenoid tissue reaction may also show features of another tissue reaction pattern as a major or minor feature. These conditions are listed in **Table 3.3**.

Direct immunofluorescence of involved skin shows colloid bodies in the papillary dermis, staining for complement and immunoglobulins, particularly IgM. An irregular band of fibrin is present along the basal layer in most cases. Often there is irregular extension of the fibrin into the underlying papillary dermis (**Fig. 3.5**). One study found colloid bodies in 60% of cases of lichen planus, whereas fibrin was present in all cases.[193] Immunofluorescent analysis of the basement membrane zone, using a range of antibodies, suggests that disruption occurs in the lamina lucida region.[194] Other studies have shown a disturbance in the epithelial anchoring system.[195]

Electron microscopy

Ultrastructural studies have confirmed that lymphocytes attach to basal keratinocytes, resulting in their death by apoptosis.[4,5,196] Many cell fragments, beyond the limit of resolution of the light microscope, are formed during the budding of the dying cells. The cell fragments are phagocytosed by adjacent keratinocytes and macrophages.[197] The large tonofilament-rich bodies that result from redistribution of tonofilaments during cell fragmentation appear to resist phagocytosis and are extruded into the upper dermis, where they are recognized on light microscopy as colloid bodies.[198] Various studies have confirmed the epidermal origin of these colloid bodies.[199,200] There is a suggestion from some experimental work that sublethal injury to keratinocytes may lead to the accumulation of tonofilaments in their cytoplasm. Some apoptotic bodies contain more filaments than would be accounted for by a simple redistribution of the usual tonofilament content of the cell.

Differential diagnosis

The moat important distinction is between lichen planus and *lupus erythematosus*. This can be a particular problem with scalp lesions, where the infiltrates of lichen planopilaris can closely resemble the follicular involvement of lupus erythematosus (see later), or with lupus lesions that display dense superficial dermal infiltrates. Atrophic lichen planus can bear a resemblance to poikilodermatous lesions of lupus erythematosus, whereas hypertrophic lesions of discoid lupus erythematosus can resemble their hypertrophic lichen planus counterpart. In contrast to lichen planus, lupus erythematosus most often shows epidermal atrophy, persistent vacuolar change of the basilar layer rather than basal keratinocyte loss (with flattening or 'sawtoothing' of the epidermal base), basement membrane zone thickening (especially in lesions of at least 6 months' duration), a deep as well as superficial dermal infiltrate that involves vessels and sweat glands as well as follicles, and often interstitial dermal mucin deposition. In addition, a degree of panniculitis is seen in a significant number of lupus cases, consisting of mild patchy lymphocytic infiltrates, mucin deposition, or lipoatrophy; those changes are not seen in lichen planus. The most common problems in differential diagnosis arise with *lichenoid keratoses* and *lichenoid drug eruptions*. These entities are further discussed later. Most of the other lichenoid dermatoses lack the full constellation of findings of lichen planus. *Lichenoid actinic keratosis*, or *actinic cheilitis*, shows basilar keratinocyte atypia that is disproportionate to that expected as a response to inflammation alone, and often the atypical changes extend laterally beyond the zone of most intense dermal inflammation. Fully developed *lichen sclerosus* is quite distinctive, but early disease may show a band-like superficial infiltrate partly obscuring the dermal–epidermal interface; together with vacuolar alteration of the basilar layer, this can produce an image somewhat reminiscent of lichen planus. However, the loss of basilar keratinocytes with sawtoothing or flattening of the epidermal base is often not a feature in lichen sclerosus, and dermal edema or early homogenization of papillary collagen may be evident even in early stages of the disease. *Poikilodermatous mycosis fungoides* with a heavy, band-like infiltrate could be confused with the atrophic variety of lichen planus, but atypical lymphocytes, 'lining up' of singly dispersed lymphocytes along the basilar layer, and wiry papillary dermal collagen may be identified – findings not expected in lichen planus. In *erythema multiforme* and *fixed drug eruption*, dense, band-like infiltrates obscuring the dermal–epidermal interface would be unusual. The rapid onset of these conditions usually means that the epidermis is of approximately normal thickness, and an ordinary-appearing, basket-woven stratum corneum is often preserved. Furthermore, apoptotic keratinocytes in lichen planus are usually observed at the basilar layer or within the papillary dermis, where they are often arranged in clusters; in erythema multiforme and fixed drug eruption, apoptotic keratinocytes are usually found widely scattered throughout all levels of the epidermis. Keratosis lichenoides chronica and lichen striatus often show dermal infiltrates in patchy distribution, with involvement of the mid to deep dermis and sometimes perieccrine lymphocytic infiltration.

Direct immunofluorescence can sometimes be helpful in differential diagnosis. The combination of junctional apoptotic bodies staining for IgM and a fibrin band along the dermal–epidermal junction is characteristic of lichen planus. Although it can be mimicked by other lichenoid dermatoses, these features differ from lupus erythematosus, which when positive shows particulate, thick linear, or occasionally linear deposition of immunoglobulin, C3 complement, or fibrin along the dermal–epidermal junction. Occasionally, an antinuclear antibody can be observed in the highlighting of keratinocyte nuclei with antibodies to IgG. Therefore, this procedure can be helpful in cases of lichen planus–lupus erythematosus overlap. Immunofluorescent study can also be useful when evaluating mucous membrane biopsies, where the differential diagnosis includes both lichen planus and cicatricial pemphigoid (one example is the condition known as desquamative gingivitis, which can be a manifestation of either disease). In contrast to lichen planus, cicatricial pemphigoid would show linear deposition of immunoglobulin and/or C3 complement along the epithelial–stromal interface.

LICHEN PLANUS VARIANTS

A number of clinical variants of lichen planus occur. In some, typical lesions of lichen planus are also present. These variants are discussed in further detail here.

Atrophic lichen planus

Atrophic lesions may resemble porokeratosis clinically. Typical papules of lichen planus are usually present at the margins. A rare form of atrophic lichen planus is composed of annular lesions.[201–205] It is composed of violaceous plaques of annular morphology with central atrophy.[206] Hypertrophic lichen planus has been reported at the edge of a plaque of annular atrophic lichen planus.[207] Experimentally, there is an impaired capacity of the atrophic epithelium to maintain a regenerative steady state.

Histopathology

The epidermis is thin and there is loss of the normal rete ridge pattern. The infiltrate is usually less dense than in typical lichen planus. It may be lost in the center of the lesions.

Hypertrophic lichen planus

Hypertrophic lesions are usually confined to the shins, although sometimes they are more generalized.[208] They appear as single or multiple pruritic plaques, which may have a verrucous appearance;[209] they usually persist for many years. A case from the vulvar region resembled condylomata acuminata.[210] Rarely, squamous cell carcinoma develops in lesions of long standing.[211–214] Cutaneous horns, keratoacanthoma, and verrucous carcinoma may also develop in hypertrophic lichen planus.[215–217]

Hypertrophic lichen planus has been reported in several patients infected with the human immunodeficiency virus.[218] It also occurs in patients with HCV infection.[219] It may occur in children.[220]

Histopathology

The epidermis shows prominent hyperplasia and overlying orthokeratosis (**Fig. 3.6**). At the margins there is usually psoriasiform hyperplasia representing concomitant changes of lichen simplex chronicus secondary to the rubbing and scratching. If the epidermal hyperplasia is severe, it may mimic a squamous cell carcinoma on a shave biopsy.[221]