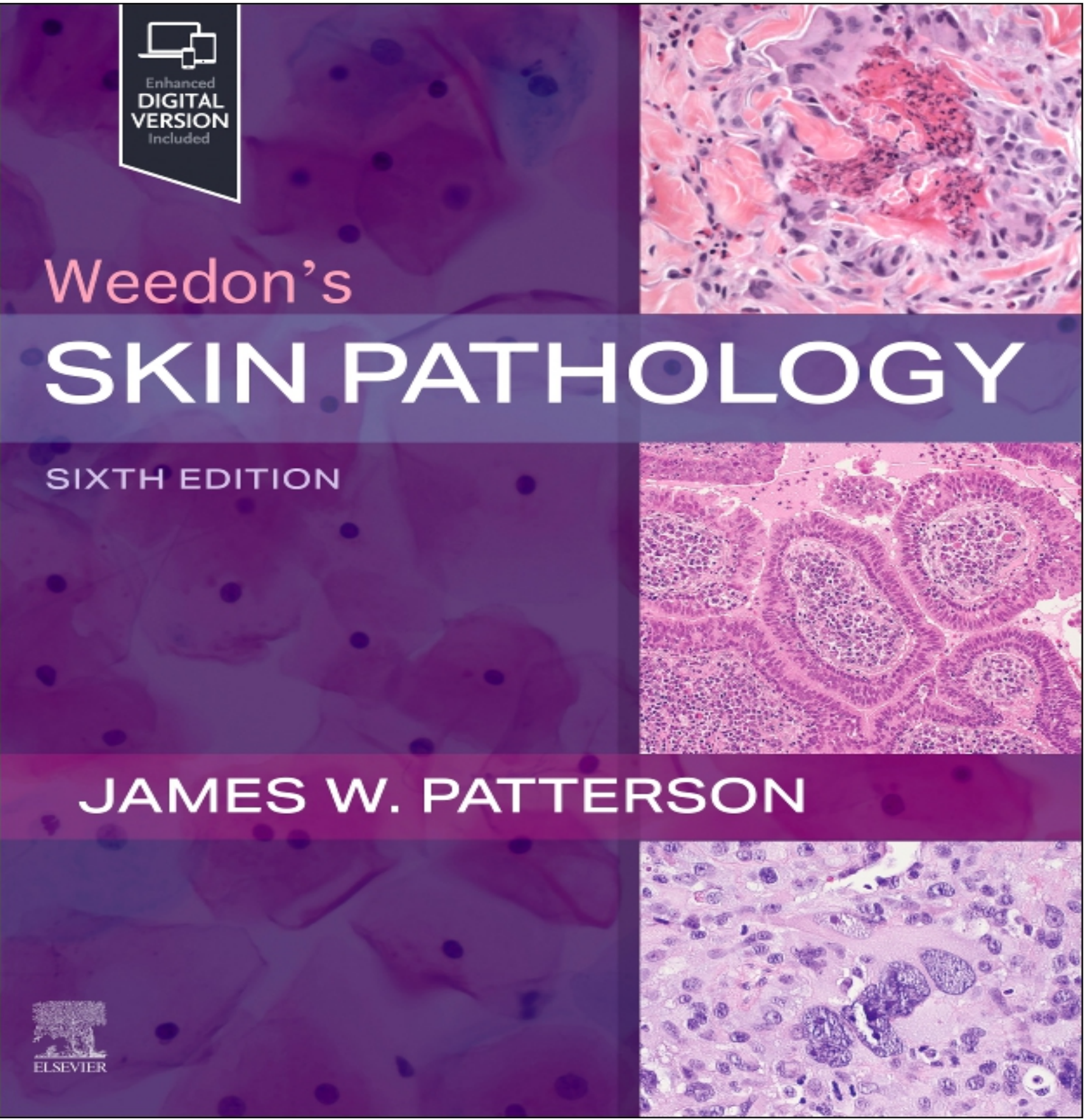

Preface

Welcome to *Weedon's Skin Pathology, 6th edition*! It has been a privilege for me to work on this volume. It has been both an educational and inspirational experience: educational, because the quantity and quality of new information in the field have been astounding; inspirational, because the new discoveries have come from all corners of the world—and all with the goals of developing a better understanding of cutaneous disease and improving the quality of life for our patients. Though some of this work may not seem to have a direct effect on diagnostic histopathology (yet), all of it, sooner or later, in one way or another, **will** have an impact, and mostly for the good.

Though there is much new information in the basic sciences that form the bedrock for our specialty and are an important part of this book, the emphasis continues to be on practical histopathology—still often the "gold standard" for determining the diagnosis of cutaneous diseases and providing guidance for their subsequent evaluation and management. Differential diagnosis has been a focus, information on dermoscopy and confocal laser microscopy has again been included, and a number of new figures have been added.

My thanks go to my colleagues: Dr. Greg Hosler, who has again revised the chapter on melanocytic lesions and provided much needed advice on the chapters related to tumors, and Dr. Karyn Prenshaw, who has helped immeasurably in the organization and provision of new figures. Many of the new photomicrographs were contributed by these two special individuals. My deep appreciation goes to Katie DeFrancesco, Belinda Kuhn, and the staff of Elsevier for their patience and support, and of course to Dr. David Weedon. And none of this would be possible without the encouragement of my wife Julie, my son Wyatt, and our daughter-in-law Elizabeth.

1 What's new in the sixth edition

As was true in the fifth edition, the purpose of this chapter is to provide *selected* highlights of new information (or, in some cases, revitalized old information) that has become available in the realm of dermatopathology, along with the chapter where each one (and its references) can be found in this volume. The emphasis is on histopathology, immunohistochemistry, and differential diagnosis.

It is not intended to be a comprehensive summation of all such information, and of course, individual readers may disagree on the choices made, but at least this will give some indication of the depth and breadth of new knowledge that has been generated by colleagues throughout the world since the previous edition.

CHAPTER 4: THE LICHENOID REACTION PATTERN ("INTERFACE DERMATITIS")

Subtle forms of **lichen planopilaris** can be found in areas of androgenetic alopecia, targeting miniaturized vellus follicles. These include **fibrosing alopecia in a pattern distribution (FAPD)** and **cicatricial pattern hair loss (CPHL) of Olsen**, the latter occurring in the setting of female pattern hair loss with pencil eraser—sized areas of scarring. Both show loss of sebaceous glands, a mild peri-isthmic lymphocytic infiltrate around miniaturized hair follicles, fibrotic collagen tracts, and dermal melanophages (see Chapter 4, Lichen Planopilaris).

In the differential diagnosis of *lichen planopilaris*, the finding of dermal clusters of CD123 positive plasmacytoid dendritic cells is a sensitive and specific predictive finding for **lupus erythematosus** (see Chapter 4, Lichen Planopilaris).

Collagenous spherulosis has been reported in **lichenoid keratosis**. This consists of eosinophilic globules in the basilar layers of the epidermis that resemble Civatte bodies but are larger and more fibrillar, the fibrils arranged in a star-shaped configuration. These structures stain blue with trichrome stain (see Chapter 4, Lichen Planus—Like Keratosis).

CHAPTER 5: THE PSORIASIFORM REACTION PATTERN

The ñ sign is a visual clue to the diagnosis of **psoriasis**. The tilde above the "n" represents separation of laminar parakeratotic stratum corneum from the underlying epidermis, whereas the "n" itself represents epidermal hyperplasia with elongated rete ridges. Necrotic keratinocytes are sometimes found in the upper third of the epidermis in psoriasis and are much less common in either **psoriasiform dermatitis** or **normal skin** (see Chapter 5, Psoriasis).

Findings that can be helpful in differentiating **guttate psoriasis** from **pityriasis rosea** include hyperkeratosis, neutrophils in parakeratotic mounds, dilated papillary dermal capillaries, and a high ratio of epidermal to dermal Langerhans cell counts—all characteristic of psoriasis (see Chapter 5, Psoriasis).

In the differentiation of **psoriasis** from **acute generalized exanthematous pustulosis** (AGEP), the latter can feature eosinophilic spongiosis, vacuolar alteration of the basilar layer, dermal eosinophilia, smaller intraepidermal pustules, apoptosis, and underlying vasculitic changes. But favoring pustular psoriasis is the finding of more than 10 intradermal CD161 positive cells, intraepidermal and perivascular CD123 positive cells, and positive myxovirus resistance protein A (MxA) among dermal inflammatory cells (see Chapter 5, Pustular Psoriasis).

Eosinophils and plasma cells may be present in the inflammatory infiltrates associated with **pityriasis rubra pilaris** (PRP). One study showed that 17% of cases had "tissue eosinophilia"; those with tissue and/or peripheral eosinophilia were more likely to be older than those without and to have widespread disease. Plasmacytoid dendritic cells are also present in the inflammatory infiltrates of most PRP cases (see Chapter 5, Pityriasis Rubra Pilaris).

CHAPTER 6: THE SPONGIOTIC REACTION PATTERN

The association of **allergic contact dermatitis** and **erythema multiforme** (EM) has been placed into two categories: EM-like allergic contact dermatitis, in which eczematous lesions at the site of contact develop target-like, erythematous, urticarial lesions, and EM *following* allergic contact dermatitis. In EM-like allergic contact dermatitis, in contrast to EM *following* allergic contact dermatitis, microscopic findings include spongiosis, exocytosis, limited keratinocyte necrosis, intraepidermal bullae (when bullae occur), and limited basilar vacuolization (see Chapter 6, Allergic Contact Dermatitis).

In **facial discoid dermatitis**, a condition that has overlapping features with psoriasis and seborrheic dermatitis, microscopic features include psoriasiform hyperplasia, compact hyperkeratosis with follicular plugging, a preserved granular cell layer with alternating orthokeratosis and parakeratosis (resembling PRP), and a superficial perivascular lymphohistiocytic infiltrate. Atrophy of sebaceous lobules has also been found—a feature shared with psoriasis and some cases of seborrheic dermatitis (see Chapter 6, Seborrheic Dermatitis).

A four-point checklist has been proposed for differentiating **palmoplantar pustulosis** from **pompholyx**: (1) vesicles lacking spongiosis and (2) microabscesses on the edges of vesicles favor palmoplantar pustulosis, whereas (3) vesicles with surrounding spongiosis and (4) neutrophils confined to the tops of vesicles favor pompholyx. Another study by the same group identified high levels of hyaluronate accumulation in pompholyx epidermis and acantholytic keratinocytes within vesicles covered with hyaluronic acid (see Chapter 6, Pompholyx).

CHAPTER 7: THE VESICULOBULLOUS REACTION PATTERN

The **Colombia variant of endemic pemphigus foliaceus** (EPF), also called **El Bagre-EPF**, shares features with pemphigus erythematosus. It may show antigenic reactivity to skin and other organ systems, such as the *areae compositae* of the heart, and some of these also presented with left ventricular hypertrophy. The membrane attack complex (MAC: C5b-9) is strongly expressed in lesional skin from patients with this Colombia variant of endemic pemphigus, and there is a correlation between greater intensity of MAC staining and higher autoantibody titers. Attachment of C5b-9 to plasma membranes may result in exposure of tissue antigens, permitting the targeting of these normally protected antigens by dysregulated lymphocytes (see Chapter 7, Pemphigus Erythematosus).

Cases presenting clinically as **pyodermatitis-pyostomatitis vegetans** (PPV), associated with inflammatory bowel disease, have shown intercellular immunoglobulin (Ig)A deposition, and additional cases with intercellular IgA deposits were reported in a recent review. It remains to be determined whether these cases showing IgA deposits are truly PPV or examples of *IgA pemphigus vegetans*, one of the types of IgA pemphigus. Similar concerns arise in the few cases designated as PPV that were reported to have intercellular IgG and C3 on direct immunofluorescence (IF) and/or anti-epithelial antibodies on indirect IF, which could actually represent examples of pemphigus vegetans (see Chapter 7, Pemphigus Vegetans).

There has been a long-held belief that there is a high false-negative rate of direct IF studies for pemphigoid performed on skin from the lower extremities. This issue has been recently reinvestigated in a study of 79 patients with IF studies from various anatomic sites, including the lower extremities;

the authors found that there was no statistically significant difference among anatomic sites in terms of false-negative IF studies (see Chapter 7, Subepidermal Blisters With Eosinophils, Bullous Pemphigoid).

CHAPTER 8: THE GRANULOMATOUS REACTION PATTERN

There is evidence for the presence of *Cutibacterium* (formerly *Propionibacterium*) *acnes* in cutaneous granulomas of **sarcoidosis**. They have been identified in several studies with immunohistochemistry using a *C. acnes* antibody. This organism is said to be "specific" for sarcoidal granulomas because it is not found in cutaneous granulomas of other types, although it can be identified outside the granulomas in both sarcoidosis and nonsarcoid controls. The presence of this organism may also explain the efficacy of minocycline in some cases of cutaneous sarcoidosis (see Chapter 8, Sarcoidosis).

A recent study found that one-third of cases of **interstitial granuloma annulare** contained eosinophils and plasma cells. The presence of plasma cells in an interstitial dermatitis is also suggestive of **early inflammatory morphea**. **Cutaneous borreliosis** also has resemblances to interstitial granuloma annulare; these may only be differentiated by clinicopathological correlation, polymerase chain reaction (PCR), or serological studies. A granuloma annulare–like eruption has been described in the cutaneous infiltrate of **chronic lymphocytic leukemia**. That case showed interstitial granulomas and elastophagocytosis, but a B-cell infiltrate was also found in which the cells expressed CD20 and CD5 (see Chapter 8, Granuloma Annulare).

Melkersson–Rosenthal syndrome should be distinguished from **Morbihan disease**. Both are parts of a spectrum of chronic lymphedema of the face, although Morbihan disease is considered a manifestation of rosacea. Microscopically, there is considerable overlap between the two conditions, including lymphedema and noncaseating granulomas, which may be found adjacent to or within lymphatics. However, Morbihan disease may also present with scattered papules or pustules, biopsies of which may show *Demodex* folliculitis, in addition to the other findings (see Chapter 8, Melkersson–Rosenthal Syndrome).

CHAPTER 9: THE VASCULOPATHIC REACTION PATTERN

The key to the histopathological diagnosis of **livedo reticularis** is obtaining a sufficiently deep biopsy to include the deep dermis and a portion of the subcutis. Recent studies indicate that there are no significant differences in vascular changes between clinically white and violaceous areas and that sampling of both may increase diagnostic yield. Changes include vessel wall thickening, erythrocyte aggregation, arterial luminal obliteration, vasculitis, thrombosis, or fibrinoid changes of the vessel wall. The type of change may sometimes provide a clue as to the nature of the underlying disease—for example, vasculitis in polyarteritis nodosa or endothelitis and thrombus formation in Sneddon's syndrome (see Chapter 9, Livedo Reticularis).

There has been debate about a possible link between **histiocytoid Sweet's syndrome** (HSS) and hematological disorders, including myelodysplastic syndromes. The most recent investigation on this subject shows that HSS is more commonly associated with myelodysplastic syndrome and hematological malignancies than is "classical" neutrophilic Sweet's syndrome, and it may also be associated with lymphoid malignancies. The authors pointed out that 5% of cases of HSS were only present in the subcutis, indicating the need for deeper biopsies for diagnosis (see Chapter 9, Sweet's Syndrome).

CHAPTER 10: DISORDERS OF EPIDERMAL MATURATION AND KERATINIZATION

Under polarized light, the hairs of **Netherton's syndrome** show a characteristic banding pattern, with the bands ranging from 0.1 to 1.0 mm in width. This banding pattern is not seen in normal controls or in patients with atopic dermatitis. In one study, it was more frequently observed than trichorrhexis invaginata, and it was found even in patients in whom trichorrhexis invaginata was not identified (see Chapter 10, Netherton's Syndrome).

Examples of **porokeratosis** with lichenoid changes can sometimes be mistaken for **lichenoid keratosis**. This issue was explored recently, and it was found that of 104 cases of lichenoid keratosis selected for review, 10 of them (9.6%) had sufficient features to qualify for a rediagnosis of porokeratosis (see Chapter 10, Porokeratosis and Variants).

Lesions of **hypergranulotic dyscornification** show prominent hyperkeratosis, which is orthokeratotic in 80% and parakeratotic in 20%; parakeratosis is focal and arranged in tiers above areas of papillomatosis. The granular layer consists of plump, dark keratinocytes with clumping of keratohyaline granules; these overlie cells in the spinous layer that have a pale hue. Mounds of anucleate, glassy eosinophilic corneocytes overlie both epidermal papillations and valleys; they were *not* found in 20% of the cases of Roy et al. Koilocytes (cells with perinuclear haloes) are absent in hypergranulotic dyscornification, and staining for human papillomavirus (HPV) is consistently negative. The findings that are relatively unique to hypergranulotic dyscornification include the dull, eosinophilic, anucleate cell "shadows," sometimes with haloes, arranged in broad columns above the hypergranulosis, and discrete foci of bright pink cytoplasm in the spinous layer (see Chapter 10, Hypergranulotic Dyscornification).

CHAPTER 11: DISORDERS OF PIGMENTATION

A recent report of a case of **Chédiak–Higashi syndrome** described small melanin clumps throughout the cortex and medulla of a hair shaft as well as polychromatic birefringence of the hair shaft with polarized microscopy, suggesting that hair shaft examination may be a helpful ancillary test in reaching or confirming a diagnosis of Chédiak–Higashi syndrome, particularly in circumstances where molecular testing is not readily available (see Chapter 11, Chédiak–Higashi Syndrome).

Despite the putative role of *C. acnes* in **progressive macular hypomelanosis**, a definite causal role for type III strains has not been proven. There are reports of progressive macular hypomelanosis in which *C. acnes* has not been found. This raises the possibility that the bacterium may initiate a sequence of events leading to hypopigmentation, although no longer detectable within lesions at the time of testing, or that *C. acnes* is one of several different factors that can promote the development of this disorder (see Chapter 11, Progressive Macular Hypomelanosis).

CHAPTER 12: DISORDERS OF COLLAGEN

In **morphea**, loss of CD34 expression within an interstitial dermal lymphoid infiltrate can be a helpful clue to the diagnosis. The degree of CD34 expression is inversely correlated to the degree of dermal sclerosis in this disease. When there is a prominent interstitial dermal lymphocytic infiltrate, the inflammatory phase of morphea could be confused with a variety of other conditions, including **Schamberg's disease** and **interstitial mycosis fungoides.** In those scenarios, the loss of CD34 and the presence of plasma cells

in the dermal infiltrate favor the diagnosis of morphea (see Chapter 12, Morphea).

Medallion-like dermal dendrocyte hamartoma has some resemblances to **fibroblastic connective tissue nevus** and has been considered by some to be an overlapping entity. However, in addition to the characteristic clinical medallion shape of the former lesion, microscopic differences include papillomatosis, patchy/weak CD34 staining of constituent cells, displaced (i.e., dermal) adipose tissue, and entrapped appendages in fibroblastic connective tissue nevus, whereas atrophy, papillary dermal involvement, and diffuse/strong CD34 staining most often characterize medallion-like dermal dendrocyte hamartoma (see Chapter 12, Fibroblastic Connective Tissue Nevus).

There are some clinical similarities between **fibroblastic rheumatism** (FR) and **multinucleate cell angiohistiocytoma** (MCAH). There can also be some histopathological similarities, although there are also distinguishing features. Both FR and MCAH feature spindle cells, variously described as fibroblastic, myofibroblastic, or fibrohistiocytic. In FR, these are arranged in fascicles (or randomly arranged in paucicellular areas) and are factor XIIIa and CD68 negative, whereas they are less conspicuous and positive for factor XIIIa and CD68 in MCAH. Multinucleated giant cells have been found in cases of FR but are generally not present, whereas they are an essential feature of MCAH, where they are large and angulated, with ringed or clumped nuclei and basophilic cytoplasm. Finally, blood vessels are not a prominent feature of FR (see Chapter 12, Fibroblastic Rheumatism).

CHAPTER 13: DISORDERS OF ELASTIC TISSUE

In **pseudoxanthoma elasticum** (PXE), there is a good correlation between the severity of the clinical change and the histology. However, biopsies from clinically unaffected skin of patients with PXE can show the characteristic elastic fiber changes. Combination cases show elastic tissue changes of PXE together with expected findings of **calciphylaxis** and/or **nephrogenic systemic fibrosis**. Chen et al. have suggested that the finding of PXE-like changes can be a useful clue to the diagnosis of calciphylaxis in suspected cases where suboptimal (small and shallow) skin biopsies have been submitted (see Chapter 13, Pseudoxanthoma Elasticum).

The subepidermal bullae that sometimes arise in **erythema ab igne** can mimic localized, infiltrate-poor pemphigoid. However, in addition to negative direct IF, workup in one case showed no abnormalities on enzyme immunoassays for antidesmoglein-1, antidesmoglein-3, and anti-BP180 NC IgG (see Chapter 13, Erythema Ab Igne).

Several cases of **papillary dermal elastolysis** have followed treatment with nivolumab and cabiralizumab immunotherapy (respectively, a PD-1 inhibitor and a colony-stimulating factor-1 inhibitor). These lesions presented as atrophic "punched-out" macules over the neck, trunk, and lower extremities. These particular cases of papillary dermal elastolysis show diminished elastic fibers in the papillary dermis but also feature a perivascular and interstitial infiltrate in the superficial and mid-dermis composed mainly of histiocytes but also containing some lymphocytes and eosinophils; there is also markedly increased dermal mucin deposition (see Chapter 13, Papillary Dermal Elastolysis).

CHAPTER 14: CUTANEOUS MUCINOSES

A recent study of **self-healing juvenile cutaneous mucinosis** has pointed out some clinical resemblances to juvenile dermatomyositis, including nodular lesions, periorbital edema, and sometimes arthritis and arthralgia. Several microscopic features overlap as well, including dermal mucin deposits and the development of panniculitis. However, dermatomyositis lacks the finding of ganglion cells, while at the same time, it has interface changes that are lacking in self-healing juvenile cutaneous mucinosis (see Chapter 14, Self-Healing Juvenile Cutaneous Mucinosis).

Osseous sclerotic bodies with entrapment of elastic fibers are sometimes observed in **nephrogenic systemic fibrosis** (NSF) and, when present, are strongly suggestive of the diagnosis. These are considered variations of the so-called "lollipop lesion"—sclerotic, amorphous eosinophilic bodies, sometimes calcified, that appear to be pierced by elastic fibers. Gadolinium has been identified in sclerotic bodies using a mass spectrometry technique. Sclerotic bodies have also been a key feature in several other examples of a lesion termed *gadolinium-associated plaque* (GAP), which has presented both as erythematous plaques and as ill-defined hyperpigmented nummular patches. These patients did not have NSF. Microscopically, sclerotic bodies, with or without calcification, represented the predominant histopathological feature, together with varying degrees of fibrosis and CD34+ cells. It is not yet clear whether gadolinium-associated plaques represent a *forme fruste* of NSF or a distinct entity (see Chapter 14, Nephrogenic Systemic Fibrosis).

Two apparently rare variants of **mucinous nevus** are **mucinous eccrine nevus** and **follicular mucinous nevus**. Mucinous eccrine nevi can show an essentially normal epidermis or varying degrees of hyperkeratosis, acanthosis, and papillomatosis. The characteristic findings are proliferations of eccrine ducts and glands, sometimes hyperplastic, surrounded by abundant mucin that stains positively with colloidal iron, toluidine blue, and alcian blue at pH 2.5, hyaluronidase sensitive. Follicular mucinous nevi feature hyperkeratosis, papillomatosis, acanthosis, and abundant colloidal iron and alcian blue–positive mucin in the superficial dermis and surrounding hair follicles, associated with spindled fibroblasts. An absence of collagen and elastic fibers has been found in the mucinous areas, the latter demonstrated by negative Verhoeff–van Gieson (VVG) staining. The spindled fibroblasts are CD34 positive (see Chapter 14, Nevus Mucinosus).

CHAPTER 15: CUTANEOUS DEPOSITS

A number of the microscopic features of **calciphylaxis** have been reported in other conditions, including Monckeberg's sclerosis, lupus panniculitis, pancreatic panniculitis, and peripheral artery disease/atherosclerosis. In a retrospective review, the following histopathological changes were found more often in calciphylaxis than in these other disorders: stippled or chunky calcification, capillary calcification, small and medium vessel calcification, calcification of any vessel size, vascular tunica media calcification, and vascular thrombosis. Calciphylaxis involves the tunica media of small vessels and, on imaging, shows a finely branching, net-like pattern of calcifications in the subcutis, whereas Monckeberg's sclerosis is distinguished by involving larger muscular arteries and muscular tunica media and by showing a "railroad track" calcification on imaging. Atherosclerosis is found incidentally as discrete irregular lesions involving the tunica intima of larger arteries (see Chapter 15, Calciphylaxis).

The association of **nodular or plaque-like cutaneous amyloid deposits with repeated insulin injections**, once considered a rare event, has now been reported frequently (over 75 cases are known); at least 10 case reports or small series have appeared since 2019. These occur with several different forms of insulin; human insulin is apparently the most common form found in these amyloid deposits. In addition to Congo red–positive amyloid material, strong anti-insulin antibody staining is found within the amyloid deposits. In at least four cases, there were also acanthosis nigricans-like changes overlying the nodules or plaques; on biopsy, these showed hyperkeratosis, papillomatosis, and mild acanthosis. Presumably, activation of insulin-like growth factor receptors by insulin is responsible for these changes (see Chapter 15, Nodular Amyloidosis).

Pseudo-ochronosis is a yellow-brown (ochre-colored) pigment involving dermal collagen bundles or elastic fibers in localized argyria, first reported by Robinson-Bostom et al. In the recent case of Georgiadou et al., there was a history of long-term silver exposure in the involved site on a finger,

and transmission electron microscopy and energy-dispersive X-ray spectroscopy demonstrated, respectively, the presence of electron-dense particles ranging up to 150 nm in diameter and their identity as silver. That case also showed more typical deposits of small black-silver granules along the basement membrane zones of eccrine glands and the dermal-epidermal junction. The reason for the ochre coloring has not been fully explained, but it may be a feature of metal granule deposition in general and not necessarily specific to silver (see Chapter 15, Ochronosis).

CHAPTER 16: DISEASES OF CUTANEOUS APPENDAGES

The identity of the **trichodysplasia spinulosa polyomavirus** (TSPyV; a member of human polyomavirus 8) has been confirmed by molecular methods. The seroprevalence increases with age and can be detected in 70% of adults, although disease occurs in only a small percentage of individuals, mostly those who are immunocompromised and especially in transplant patients. The virus is detected in nuclei by immunostaining for SV40 virus, which cross-reacts with several human polyomaviruses, including TSPyV, and can also be found using in situ hybridization for TSPyV ribonucleic acid (RNA) (see Chapter 16, Viral Folliculitis).

By energy-dispersive X-ray spectroscopy, the crystals found in the keratinous material of **necrotizing infundibular crystalline folliculitis** (NICF) were shown to be organic in nature, containing carbon but neither calcium nor sodium, and immunohistochemical results argued against keratin tonofilament origin. However, other materials have been found in different patients. Kossard has proposed that NICF is the expression of altered follicular repair pathways. These pathways include epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and programmed death-1 (PD-1), along with a population of regulatory T cells. This would explain reports of NICF in patients who have received EGFR, VEGF, or PD-1 *inhibitors* for the treatment of metastatic carcinoma (see Chapter 16, Miscellaneous Folliculitides).

In a recent case of **mucinous syringometaplasia**, mucinous metaplasia was present in an epidermal invagination, surrounded and partly obscured by adjacent hyperkeratosis and acanthosis. Another case, presenting as an alopecic plaque in the occipital scalp of a newborn, showed hypertrophic scar and, in the deep aspect of the scar, a proliferation of eccrine ducts and glands. In a few dilated ducts, surrounded by an outer layer of myoepithelial cells, there was a columnar inner epithelial lining composed of cells with intracytoplasmic mucin and apical cilia. The authors termed this *ciliated and mucinous adenomatous syringometaplasia* and speculated that it may represent the "missing link" in the histogenesis of a cutaneous eccrine ciliated cyst (see Chapter 16, Eccrine Metaplasias).

CHAPTER 17: CYSTS, SINUSES, AND PITS

The distinction of **proliferating trichilemmal tumor (PTT)** (particularly, **malignant PTT** [MPTT]) from squamous cell carcinoma can be difficult, especially if evidence of origination from a trichilemmal cyst, or clear-cut trichilemmal keratinization, is difficult to discern. P53 staining is not completely reliable for this purpose, nor is Ki-67 expression, although strong staining with the latter may have some value as a marker for tumor progression in MPTT. Certain cytokeratins—particularly AE13 and AE14—tend to be positive in PTTs but not in squamous cell carcinoma. CD34 is a marker for outer root sheath differentiation and is reportedly often positive in PTT but negative in squamous cell carcinoma. However, a recent review found that four of nine MPTTs were negative for CD34, and another case had less than 1% expression. The authors speculate that expression of CD34 may correlate with the degree of tumor differentiation. Calretinin, another marker of outer root sheath differentiation, might also be a useful stain in this differential diagnostic scenario; a negative result with this marker was used, in part, to support a diagnosis of squamous cell carcinoma over MPTT in a recent case (see Chapter 17, Proliferating Trichilemmal Tumor and Malignant Proliferating Trichilemmal Tumor).

CHAPTER 18: PANNICULITIS

There have been several recent reports of "**pancreatic panniculitis,**" with typical clinical and microscopic features, developing in patients with **systemic lupus erythematosus** but without evidence of pancreatic disease. There has also been a small case series of three nonlupus patients without evident pancreatic disease but with characteristic pancreatic panniculitis lesions. Although the cause of the panniculitis was unclear in these cases, several of the patients had decreased renal function and were receiving hemodialysis; it is known that there can be elevated amylase and lipase levels in these patients. Other contributing factors may have included prior vascular damage or release of adipokines (see Chapter 18, Pancreatic Panniculitis).

Overlap cases have been described that have microscopic features of both **lupus panniculitis** and localized scleroderma ("**sclerodermic lupus profundus**"). In a recent case, in addition to the histopathological features of lupus panniculitis, there was also fibrosis of the deep dermis and subcutaneous septa, with reduced CD34 expression (as seen in scleroderma) but, unlike scleroderma, a lack of smooth muscle actin expression among fibroblasts. Also, staining for human myxovirus resistance protein 1 (MxA) showed significant positivity, particularly in endothelium, inflammatory cells, and adnexal epithelia; positivity for MxA is characteristic of lupus panniculitis but not of localized scleroderma (morphea) (see Chapter 18, Lupus Panniculitis).

A recently reported case that had been treated for 10 years as **lupus panniculitis** was found to be associated with an *HAVCR2* mutation. This gene encodes hepatitis A virus cellular receptor 2 (T-cell immunoglobulin mucin receptor 3), a Th1-specific cell surface protein that, among other things, regulates macrophage activation and promotes immunological tolerance. Mutation of this gene has now been associated with a number of cases of subcutaneous panniculitis-like T-cell lymphoma (see Chapter 18, Lupus Panniculitis).

CHAPTER 19: METABOLIC AND STORAGE DISEASES

A patient with **Olmsted's syndrome** and essential thrombocytosis was misdiagnosed as acrodermatitis enteropathica. Zinc levels in this case were normal. Although the microscopic descriptions of two skin biopsies highlighted features that could overlap with those of acrodermatitis enteropathica, the characteristic pallor of cells in upper layers of the epidermis seen in the latter disorder was not reported (see Chapter 19, Acrodermatitis Enteropathica).

In the microscopical interpretation of **glucagonoma syndrome**, the most distinctive pattern is the presence of pale, vacuolated keratinocytes in the upper epidermis, leading to focal or confluent necrosis. This process has been termed *necrolysis*. This horizontal zone, sandwiched between keratinocytes with their basophilic nuclei below and eosinophilic parakeratosis above, creates the so-called "tricolor flag" image that is seen in skin lesions due to nutritional deficiencies and necrolytic acral erythema, as well as necrolytic migratory erythema (see Chapter 19, Glucagonoma Syndrome).

CHAPTER 21: CUTANEOUS DRUG REACTIONS

Changes resembling *Cryptococcus* organisms have been described in a number of the recent case reports of **iododerma**. This finding was originally described by Ko et al. in neutrophilic dermatoses associated with

hematological malignancies or immune dysregulation. Clear spaces surround acellular bodies that, on transmission electron microscopy, appear to be compatible with residual degenerated nuclei. These structures fail to stain with the usual methods for fungi, and in one report, the nuclei were immunohistochemically positive for the transcription factor SPI1, a marker for histiocytes and dendritic cells (see Chapter 21, Halogenodermas).

A late sequela of **DRESS** (*d*rug *r*ash with *e*osinophilia and *s*ystemic *s*ymptoms) **syndrome** can be thyroid dysfunction, including Hashimoto's thyroiditis, Graves' disease, and nonspecific hypothyroidism. Recurrences of DRESS have been reported; they typically present with both higher fevers and peak levels of eosinophils. Survival of those patients with recurrences is 71%; poor prognosis associated with a recurrence is linked to viral reactivation (e.g., human herpesvirus 6 [HHV-6]), severe involvement of internal organs, and hematological abnormalities (see Chapter 21, Drug Hypersensitivity Syndrome).

CHAPTER 22: REACTIONS TO PHYSICAL AGENTS

Lymphoid follicles have been detected in about 64% of biopsies of the cheilitis associated with **actinic prurigo**. Application of toluidine blue prior to skin biopsy can aid in detecting areas in which lymphoid follicles are present, in that this agent selectively stains acidic components of tissues that are incorporated into DNA and RNA—higher concentrations of which are found in these lymphoid follicles. A similar follicular pattern is often present in the conjunctiva (see Chapter 22, Actinic Prurigo).

CHAPTER 24: BACTERIAL AND RICKETTSIAL INFECTIONS

In a case of **phlebitic tuberculid** (termed *nodular granulomatous phlebitis*), there was granulomatous inflammation involving a medium-sized vessel in the lower reticular dermis, with caseous necrosis filling the lumen, surrounded by epithelioid histiocytes, Langhans-type giant cells and lymphocytes; no internal elastic lamina was seen with VVG stain, indicating its identity as a vein. Staining for acid-fast bacilli was negative, and tissue culture was negative for mycobacteria. The patient had a pulmonary nodule and sputum cultures that grew *Mycobacterium tuberculosis*. With antituberculous treatment, the skin lesions resolved (see Chapter 24, Tuberculids).

Two methods of staining for **leprosy** lesions have been compared in a study of 40 patients; the study showed that fluorescent staining (using the Truant, or auramine-rhodamine, stain) is more sensitive than a modified Fite—Faraco method in detecting acid-fast bacilli in tissue specimens of leprosy cases (see Chapter 24, Leprosy).

A recent case report described a patient with anesthetic skin lesions and a facial droop who proved to have **sarcoidosis**, not **leprosy**, and showed a granulomatous dermal infiltrate exclusively surrounding small cutaneous nerves. The authors of a commentary on this article had previously performed a study of 76 sarcoidosis patients and found that 23% had perineural granulomas on biopsy (see Chapter 24, Leprosy).

CHAPTER 25: SPIROCHETAL INFECTIONS

Although for years it had not been possible to cultivate and maintain ***Treponema pallidum*** on artificial media, *T. pallidum* subsp. *pallidum* Nichols has now been cultured continuously for over 3 years in an Sf1Ep culture system. This system requires cottontail rabbit epidermal cells (Sf1Ep cells) in appropriate numbers and, among other components, a complex nutrient medium (CMRL 1066 and M199) and fetal bovine serum. Another strain of pathogenic significance, *T. pallidum* subsp. *endemicum*, the causative organism in endemic syphilis (bejel), can apparently also be maintained in this system. The causative agent of yaws, *T. pallidum* subsp. *pertenue*, has not yet been successfully cultured (see Chapter 25, Treponematoses).

A recent case report and literature review found that the most common microscopic findings in **congenital syphilis** are perivascular or lichenoid infiltrates containing a variety of cell types (neutrophils, lymphocytes, histiocytes, eosinophils, plasma cells) and intraepidermal vesicles or bullae containing neutrophils with or without eosinophils. Other features have included psoriasiform acanthosis, parakeratosis, scattered dyskeratotic keratinocytes, endothelial swelling, or leukocytoclastic vasculitis. The features overlap with those of secondary syphilis in adults, although intraepidermal vesicles or bullae appear to be more common among congenital cases, whereas endothelial swelling and dyskeratotic keratinocytes are more often found in cases of secondary syphilis. Significantly, plasma cells are variable in both of these categories of cutaneous syphilis (see Chapter 25, Congenital Syphilis).

CHAPTER 26: MYCOSES AND ALGAL INFECTIONS

Two particular semiotic tests can be used to demonstrate the fine scale that is characteristic of **tinea (pityriasis) versicolor**: the scratch sign, attributed to Besnier, and the lateral stretching sign, known as the *Zireli sign*. Dermatographism can also be demonstrated in areas involved with pityriasis versicolor. In one study, 27 of 30 cases had positive dermatographism in areas of cutaneous lesions; in all of these, *Malassezia globosa* was the causative agent. Interestingly, *M. globosa* produces a histamine-releasing antigen, MGL_1304, at a size of 29 kDa, which is secreted into sweat after conversion into a "mature" form of 17 kDa; this form induces release of histamine from basophils, particularly seen in patients with atopic dermatitis or cholinergic urticaria (see Chapter 26, Pityriasis Versicolor).

The periodic acid—Schiff (PAS) stain often stains the cell wall of ***Histoplasma*** poorly. The broad-spectrum stain, methenamine silver, is always positive. Some organisms are also acid fast. Both Ziehl—Neelsen and Fite stains have been used for this purpose. *Histoplasma* organisms stain positively with these methods in up to 50% of cases, and they are more likely to be positive in viable rather than necrotic tissue. The content of mycolic acid in their cell walls is thought to explain this property. *Blastomyces* is also acid-fast positive, but the acid-fast property is not seen in other organisms that require distinction from *Histoplasma*, such as *Leishmania* and *Candida*. In contrast to the bright pink cytoplasmic staining of *Histoplasma* organisms with Ziehl—Neelsen, *Cryptococcus* shows a "granular magenta to purple" staining of its cell wall and capsule (see Chapter 26, Histoplasmosis).

A study of PAS, Grocott's silver, and calcofluor white stains in diagnosing **sporotrichosis** has shown sensitivities of 31%, 40%, and 74%, respectively. In addition to the high sensitivity of the calcofluor white stain, the authors noted the ease of interpreting sections and the ability to restain if necessary (see Chapter 26, Sporotrichosis).

CHAPTER 27: VIRAL DISEASES

Early microscopic findings in skin biopsies of **monkeypox (mpox)** include acanthosis, with spongiosis and lymphocyte exocytosis, and a band-like inflammatory infiltrate composed of lymphocytes and some neutrophils at the junctional zone with marked papillary dermal edema. Ballooning degeneration develops, involving epidermis and also the upper portions of follicular outer root sheaths; occasionally, changes in the outer root sheath predominate. Eosinophilic, Guarnieri-type intracytoplasmic inclusions are present in affected keratinocytes. A few nuclei may have a central ground-glass appearance mimicking the inclusions of herpesvirus infections, but no true intranuclear inclusions are present. Positive immunohistochemical staining has been obtained with rabbit polyclonal anti-vaccinia virus antibody (see Chapter 27, Monkeypox).

The vesicular eruption associated with **COVID-19 infection** has been said to be **varicella**-like, but this has been disputed by Mahe et al. based on their study of three cases. The lesions are often excoriated, but itching is said to be slight to absent. Microscopically, the findings consist of a unilocular intraepidermal vesical with nonballooning acantholysis, eosinophilic dyskeratosis with a "pomegranate-like" configuration of cells, and sparing of the epidermal basilar layer (see Chapter 27, COVID-19).

CHAPTER 28: PROTOZOAL INFECTIONS

In a case series consisting of three solid organ transplant recipients with reactivated **Chagas' disease**, each had ulcerated, erythematous plaques that showed lobular panniculitis with foci of neutrophilic vasculitis on biopsy; intracellular microorganisms consistent with amastigotes of *Trypanosoma cruzi* were identified and confirmed by immunohistochemistry (see Chapter 28, Trypanosomiasis).

Finding amastigotes in routinely stained tissue sections of **cutaneous leishmaniasis** can be difficult; thus, studies from Panama, Sri Lanka, and Spain have reported detection rates of *Leishmania* organisms at 50%, 66%, and 38%, respectively. The sensitivity of histopathology can be improved through the use of immunohistochemistry and particularly PCR, which has been considered the standard for the diagnosis of cutaneous leishmaniasis. Colorimetric in situ hybridization may be another useful method for the laboratory detection of amastigotes; it has the advantage of not cross-reacting with species of fungi, as can occur with immunohistochemistry (see Chapter 28, Cutaneous Leishmaniasis).

CHAPTER 29: MARINE INJURIES

In a case of **sea urchin injury** that resulted in two biopsies, one showed sarcoidal granulomas, whereas the other, described as chronic inflammation with focal suppuration and foreign body material, on review appeared to show a somewhat palisaded arrangement of epithelioid macrophages, intermingled with neutrophils. In still another recent case, dermoscopy of the foreign bodies revealed conical shapes with striated white lines and circular shapes with radiating whitish and violaceous lines, resembling the findings reported on scanning electron microscopy. On the other hand, there is research to suggest that sea urchin–derived collagen may prove to be a useful biomaterial in skin regenerative medicine (see Chapter 29, Echinoderms).

CHAPTER 30: HELMINTH INFESTATIONS

Regarding **cysticercosis**, the larvae of ***Taenia solium*** have a predilection for subcutaneous tissues. They have been reported in the supraclavicular region (masquerading as tuberculous lymphadenitis) and the buccal mucosa. Disseminated disease has also been reported; in one case, a child from Tanzania with HIV/AIDS developed disseminated cysticercosis and Kaposi's sarcoma, both of which resolved with appropriate therapies. Successful diagnosis has resulted from fine-needle aspiration cytology. The diagnosis is made by the identification of a cystic structure consisting of a thin bladder wall and a parenchymatous component that includes the scolex of the larva, surrounded by a convoluted spiral canal; the hooklets of the scolex are less frequently identified (see Chapter 30, Cysticercosis).

CHAPTER 31: ARTHROPOD-INDUCED DISEASES

Tick bites transmit the virally induced **severe fever with thrombocytopenia syndrome (SFTS)**, reported in Japan, Korea, and the United States. The likely vector is the long-horned tick ***Haemaphysalis longicornis***. One study found that CD20+ immunoblastic cells in the region of the tick bite were positive for anti-SFTS viral nucleoprotein antibody, and they were able to detect SFTS viral RNA in the biopsy specimen by real-time PCR (see Chapter 31, Tick Bites).

The comparative value of skin scrapings versus superficial skin biopsy in the diagnosis of **scabies** has been investigated. The superficial skin biopsy involves placing a drop of cyanoacrylic adhesive on a microscopic slide, applying it to the skin surface, and slowly removing it after 1 minute. The latter method was found to be superior to scrapings, with a higher percentage of patients testing positive and 21% of patients *only* testing positive with this technique (see Chapter 31, Scabies).

CHAPTER 32: TUMORS OF THE EPIDERMIS

Seborrheic keratosis with sebaceous differentiation occurs most often in the head and neck region or on the back. There is typically a flat to plate-like horizontal arrangement of basaloid cells showing vacuolated sebocytes, singly and in small clusters, and sebaceous ducts in basal portions of rete ridges. The epidermal configuration can be flat, acanthotic, reticulated, or a combination of the latter two. The authors consider this to be the same entity as "superficial epithelioma with sebaceous differentiation" and "reticulated acanthoma with sebaceous differentiation" and argue against the use of the term *epithelioma* for these benign lesions (see Chapter 32, Seborrheic Keratosis).

In the differentiation between **actinic keratosis** and **squamous cell carcinoma**, especially in superficial biopsies, a potentially useful marker may be paraoxonase-2 (PON2), an intracellular membrane-bound enzyme that is upregulated in some tumors. With the use of immunohistochemical staining for this enzyme, there is significantly increased PON2 expression in squamous cell carcinomas on the trunk and extremities as well as the head and neck when compared to surrounding normal tissue *and* actinic keratoses (see Chapter 32, Actinic Keratoses).

Laminin-1 staining may be helpful in determining early invasion in cases of actinic cheilitis; there is strong linear basement membrane staining in cases with low-grade epithelial dysplasia, loss of laminin in squamous cell carcinoma, and intracellular laminin staining in parabasal cells in examples of actinic cheilitis with high-grade epithelial dysplasia/in situ squamous cell carcinoma (see Chapter 32, Actinic Cheilitis).

In recent years, several variants of **onychomatricoma** have been described. The **onychocytic matricoma** presents as local thickening of the nail plate that may display melanonychia. Microscopic features include acanthosis of the nail matrix, proliferation of matrical onychocytes, and sometimes a collection of pigmented dendritic melanocytes. In **onychomatricoma micropapilliferum,** there are several unique features: lack of cavitation at the proximal border of the nail plate, small sizes of cavities at the free edge of the distal nail plate, and papillated epithelial hyperplasia. The **proliferating onychomatricoma** is a verrucous lesion that can resemble squamous cell carcinoma. Microscopic findings include an infiltrative but well-differentiated squamoproliferative lesion with a lobulated to cystic growth pattern and foci of abrupt keratinization (see Chapter 32, Onychomatricoma and Variants).

CHAPTER 33: LENTIGINES, NEVI, AND MELANOMAS

There continue to be advances in understanding the molecular underpinnings of nevi and melanoma, and the molecular findings have been updated under each entity. In relation to this, a new table has been added to include commonly observed molecular events in categories of benign nevi. The discussion of ancillary testing has been expanded to address how this area is evolving.

There are some revisions to the organization of the chapter to group similar entities based on histopathology, behavior, and/or molecular events. One example is grouping clear cell sarcoma, paraganglioma-like dermal melanocytic tumor, and CRTC1-TRIM11 melanocytoma at the end under "Miscellaneous Melanocytic and Melanocytic-Like Lesions."

Finally, some nomenclature has been modified for clarity (e.g., *malignant blue nevus* is changed to *melanoma ex blue nevus*), and some World Health Organization (WHO) terminology has been added under various entities when appropriate.

CHAPTER 34: TUMORS OF CUTANEOUS APPENDAGES

Cytokeratin 17 (CK17) shows strong staining of **basal cell carcinoma** but produces different results in **desmoplastic trichilemmoma** that can be exploited in the differential diagnosis. Ber-EP4 and CD34 stains can be of help in distinguishing the **clear cell variant of basal cell carcinoma** from **trichilemmoma**. In a recent study using Ber-EP4 and CD34 stains, basal cells showed partial to diffuse membranous Ber-EP4, whereas trichilemmomas were negative. With CD34, clear cell areas of basal cell carcinomas showed either no or focal staining, whereas all cases of trichilemmoma displayed membranous CD34 staining (see Chapter 34, Trichilemmoma).

Immunostaining with lymphoid enhancer factor 1 (LEF-1) can be useful in the diagnosis of **matricoma**. This is a transcription factor, encoded by the lymphoid enhancer binding factor 1 gene *LEF1*, that binds to an important site in the T-cell receptor-alpha enhancer. It is involved in the Wnt signaling pathway and is believed to function in follicle morphogenesis. The basaloid cells of this tumor show purely nuclear positivity with LEF-1, and therefore this stain may be easier to interpret than beta-catenin (see Chapter 34, Pilomatricoma).

Spindle cell—predominant trichodiscoma/fibrofolliculoma consists of hyperplastic pilosebaceous units, with what is described as "mitt-like" sebaceous lobules at either side of the lesion and an intervening stroma of spindle cells with wavy nuclei, arranged in broad, haphazard fascicles. The stroma is myxoid, displays ropey collagen bundles, and sometimes contains islands of adipocytes. Other changes that are observed less commonly include palisaded arrangements of spindled cells and cells with hyperchromatic, pleomorphic nuclei. The constituent cells are CD34 positive and S100 negative. Entrapped S100-positive nerves may be present—part of the explanation for the previous classification of this lesion as neurofollicular hamartoma (see Chapter 34, Spindle Cell—Predominant Trichodiscoma/Fibrofolliculoma).

CHAPTER 35: TUMORS AND TUMOR-LIKE PROLIFERATIONS OF FIBROUS AND RELATED TISSUES

A recent case, designated **pleomorphic acquired digital fibrokeratoma**, featured pleomorphic cells with hyperchromatic nuclei and floret-type giant cells. These resembled the cells of pleomorphic fibroma but were negative for CD34 and positive for factor XIIIa (pleomorphic fibroma cells are CD34-positive and variably factor XIIIa positive) (133A). However, as in pleomorphic fibromas, the lesional cells were negative for retinoblastoma protein and p53 (see Chapter 35, Acral Fibrokeratoma).

In their commentary on a recent case report of **pacinian collagenoma**, Saggini and Baciorri noted the lack of distinguishing molecular characteristics between **sclerotic fibroma** and **sclerosing perineurioma**, other than loss of *PTEN* in Cowden's-associated sclerotic fibromas or the loss of *NF2* in a subset of sporadic perineurioma cases (272A, 272B). They also note that many cases reported as sclerotic fibromas have not been subjected to staining with the more recent markers for perineurial cells, GLUT-1 and Claudin-1. Because some lesions diagnosed as sclerotic fibromas do express a less sensitive perineurial marker (epithelial membrane antigen [EMA]), it seems possible if not likely that some lesions diagnosed as sclerotic fibromas may prove to be sclerosing perineuriomas with the use of these newer stains (see Chapter 35, Sclerotic Fibroma).

In a study using S100 as a marker for epidermal Langerhans cells, a high density of these cells was seen in normal and peritumoral epidermis in biopsies of **dermatofibromas**, but there was a notable decrease in Langerhans cells in the epidermis *overlying* dermatofibromas. In addition, erythroblast transformation specific (ETS)-related gene (ERG) was found to stain over 50% of the tumor cells in dermatofibromas with moderate to strong intensity, whereas its expression was diminished to absent in **dermatofibrosarcoma protuberans** (DFSP) and **hypertrophic scars/keloids** (see Chapter 35, Dermatofibroma).

CHAPTER 36: TUMORS OF FAT

Nevus psiloliparus is the name applied to subcutaneous lipomas on the scalp with overlying alopecia, one of multiple anomalies associated with **encephalocraniocutaneous lipomatosis** (**Haberland's syndrome**). Biopsies show virtually complete absence of mature hair follicles with preserved arrectores pilorum muscles and intradermal aggregates of mature adipocytes. In a recent study, horizontal sections also showed "shadow" follicular units consisting of cross-sectional columns of loosely arranged collagen and diminished elastic fibers, associated with arrectores pilorum muscles (see Chapter 36, Lipoma and Lipomatosis).

The cells of **hibernoma** are UCP1 positive. In a recent study, it was found that the multivacuolated brown fat cells of hibernomas (and many of the adjacent univacuolated cells) are strongly diffusely positive for CD10 (neprilysin). CD10 was present in only 18% of adipocytes in **atypical lipomatous tumor** or **well-differentiated liposarcoma** and was found in three of six **pleomorphic liposarcomas**; it was negative in **conventional lipoma** or **fat necrosis**. Therefore, CD10 staining may be useful in the distinction of hibernoma from these other potential mimics. One caveat, however, is that CD10 staining of surrounding fibroblastic stromal cells is common among many of these lesions and should be regarded as a nonspecific finding (see Chapter 36, Hibernoma).

CHAPTER 37: TUMORS OF MUSCLE, CARTILAGE, AND BONE

Most **cutaneous angiomyolipomas** should be regarded as **angioleiomyomas with fat** ("angioleiomyoma with adipocytic metaplasia"). The rare exception is illustrated by the case of a lesion developing in the eyelid of a 2-year-old child with tuberous sclerosis; that lesion featured spindled and epithelioid cells that were positive for smooth muscle actin and for HMB-45. This tumor, as in the case of the renal angiomyolipomas associated with tuberous sclerosis, is correctly classified as a perivascular epithelioid cell tumor, or **PEComa** (see Chapter 37, Angioleiomyoma).

The **malignant rhabdoid tumor** is composed of sheets of polygonal cells with abundant hyaline eosinophilic cytoplasm and a peripherally displaced vesicular nucleus with prominent nucleolus. PAS-positive hyaline cytoplasmic inclusions may be identified. However, there may be great variability in the histopathological image of these tumors, making diagnosis extremely difficult. For example, these tumors may be highly vascular, mimicking infantile hemangioma. When available, immunohistochemical staining for integrase interactor 1 (INI1) can be helpful, but occasionally normal INI1 expression may be found in skin; despite this, deletion of the *SMARCB1* gene may be detected by DNA analysis (see Chapter 37, Malignant Rhabdoid Tumor).

CHAPTER 38: NEURAL AND NEUROENDOCRINE TUMORS

In a recent series of nine patients with **dermal hyperneury**, none showed clinical evidence of a phosphatase and tensin homolog (*PTEN*)-related or endocrine tumor syndrome; four of these had multiple skin lesions. Lesions most often presented as flesh-colored or slightly erythematous papules; in two cases, the hyperneury was an incidental change found in another lesion. Immunohistochemistry of five tested cases, including all four with multiple lesions, demonstrated retention of PTEN expression and an absence of expression of rearranged during transfection (RET), further arguing against an association with either syndrome. Microscopically, there are large nerves, focally tortuous, with prominent perineurium (see Chapter 38, Neuromas and the Multiple Endocrine Neoplasia Syndrome).

There is an atypical variant of **cellular neurothekeoma** occurring in elderly patients. As is the case in other atypical cellular neurothekeomas, these show cells with larger, epithelioid nuclei with prominent nucleoli in a nested and fascicular arrangement, infiltration into adipose tissue, and increased numbers of mitoses. Thus far, no case of recurrence or metastasis has been reported (see Chapter 38, Neurothekoma).

Another useful marker for neuroendocrine differentiation in **Merkel cell carcinoma** is insulinoma-associated protein 1 (INSM1); it showed strong, extensive, and homogeneous expression in all 24 tested cases. The authors suggested its use as a solitary marker for neuroendocrine differentiation because of its high sensitivity and specificity for this tumor (see Chapter 38, Merkel Cell Carcinoma).

CHAPTER 39: VASCULAR TUMORS

The microscopical differential diagnosis between **papillary hemangioma** and **glomeruloid hemangioma** is important in that papillary hemangioma is unassociated with POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal plasma cell disorder, *s*kin changes) syndrome or multicentric Castleman's disease. In papillary hemangioma, papillary structures are lined by plump endothelium and contain pericytes, sometimes normal-appearing capillaries, and basement membrane–like collagen; in glomeruloid hemangioma, capillaries are arranged in aggregates resembling renal glomeruli, endothelial cells are lined by thin layers of pericytes, and capillaries are separated by polygonal stromal cells. These differentiating features are highlighted by collagen IV staining (showing thick basement membrane–like material in the papillary stalks of papillary hemangioma) and actin staining of pericytes (displaying the relative prominence of these cells within the papillary stalks of papillary hemangioma) (see Chapter 39, Papillary Hemangioma).

Immunohistochemical staining for myelocytomatosis oncogene (MYC) expression can be useful in distinguishing **atypical vascular lesions** (MYC negative) from **postirradiation angiosarcoma** (MYC positive). It may also be a useful test in determining the prognosis of **secondary angiosarcoma** (because *MYC* and *FLT4* co-amplifications are associated with shorter survivals in secondary angiosarcomas). However, neither this method nor fluorescent in situ hybridization (FISH) for *MYC* amplification has significant diagnostic or prognostic value in **primary angiosarcomas**, and they should not be used to distinguish primary angiosarcoma from benign vascular tumors (see Chapter 39, Angiosarcoma and Lymphangiosarcoma).

CHAPTER 40: CUTANEOUS METASTASES

Weak p63 and CK14, CK5, and CK17 expression have been reported in **metastatic breast carcinoma**, whereas these are strongly expressed in **sweat gland carcinomas** (see Chapter 40, Breast).

Pleural mesotheliomas rarely metastasize to the skin. They are positive for low-molecular-weight cytokeratin and express the mesothelial markers calretinin, Wilms tumor 1 (WT1), and D2-40 (see Chapter 40, Lung).

Arginase-1 has higher sensitivity and specificity for **hepatocellular carcinoma**, has increased sensitivity for poorly differentiated tumors, and is useful in distinguishing hepatocellular carcinoma from metastatic carcinomas (to the liver) and cholangiocarcinoma. Cholangiocarcinomas are immunoreactive for CK7 and possibly CK20; they do not show diffuse expression of CDX2 (see Chapter 40, Liver, Pancreas, and Gallbladder).

The most sensitive biomarker for the diagnosis of **carcinoma of the pancreas** appears to be the von Hippel–Lindau gene product pVHL; the most specific markers are galectin-1, maspin, K homology domain containing protein overexpressed in cancer (KOC), and S100P (see Chapter 40, Liver, Pancreas, and Gallbladder).

CHAPTER 41: CUTANEOUS INFILTRATES—NONLYMPHOID

Guidelines have been published for the diagnosis of **IgG4-related disease** for organs, such as the skin, that do not have clear-cut organ-specific criteria. These include (1) the presence of swelling or masses; (2) serum IgG4 levels greater than 135 mg/dL; and (3) histopathological features, including marked lymphocytic and plasmacellular infiltration and fibrosis, greater than 10 IgG4+ plasma cells per high-power field, and a ratio of IgG4+ plasma cells to total IgG+ plasma cells of greater than 40%. The diagnosis of IgG4-related disease is established when all three criteria are fulfilled, probable when (1) and (3) are fulfilled, and possible when (1) and (2) are fulfilled (see Chapter 41, IgG4-Related Disease).

In a recent study of **juvenile xanthogranuloma** (JXG), the authors concluded that CD4 (in this case, as a plasmacytoid monocyte stain rather than a stain for T-helper lymphocytes) and CD11c are reliable and highly sensitive markers for JXG. They considered factor XIIIa less consistent for this diagnosis, with often weaker expression and a higher nonreactive rate than the other two markers (see Chapter 41, Juvenile Xanthogranuloma).

A recent case report described a 10-year-old patient with clinical presentation and microscopic features resembling **progressive nodular histiocytosis**. However, elevated blood cholesterol levels led to genetic testing using next-generation sequencing. The results showed a variant in the *ABCG8* gene, confirming the diagnosis of *sitosterolemia* (phytosterolemia), an autosomal-recessive condition associated with unrestricted intestinal absorption of cholesterol and related molecules (e.g., sitosterol). The lesion was ultimately diagnosed as **tuberous xanthoma** (see Chapter 41, Progressive Nodular Histiocytosis).

CHAPTER 42: CUTANEOUS INFILTRATES—LYMPHOMATOUS AND LEUKEMIC

There has been much recent work on immunohistochemical markers for the diagnosis and prognosis of **mycosis fungoides** (MF). Among the promising agents are podoplanin (D2-40), which shows significantly increased staining in higher tumor–node–metastasis–blood (TNMB)-staged and aggressive MF cases; interleukin (IL)-17 and thymocyte selection-associated HMG BOX (TOX), which, when coexpressed, may be useful in supporting the diagnosis of MF in selected circumstances; TOX, inducible T-cell co-stimulator (ICOS), and GATA-binding protein 3 (GATA3), which also show increased expression in higher stages of the disease; and cell adhesion molecule 1 (CADM1), which is upregulated in MF compared to parapsoriasis and inflammatory dermatoses (see Chapter 42, Mycosis Fungoides and Subtypes).

An important contribution to our understanding of the differentiation between **subcutaneous panniculitis-like T-cell lymphoma** (SPTCL) and **lupus erythematosus panniculitis** (LEP) has been provided by the work of Machan et al. They performed gene-expression profiling and were able to identify differentially expressed genes when comparing cases, finding that SPTCL and LEP have distinctive molecular profiles; in addition, cases with overlapping microscopic features were found to more closely resemble LEP on a molecular basis (see Chapter 42, Subcutaneous Panniculitis-Like T-Cell Lymphoma).

Intravascular **primary effusion lymphoma** was found within a cutaneous lesion of Kaposi's sarcoma in an HIV+ adult. HHV8+ immunostaining was found both in the nuclei of the Kaposi's sarcoma lesion and within large intravascular plasmacytoid cells (see Chapter 42, Primary Effusion Lymphoma).

A comparative study of **pseudolymphomatous folliculitis** and **primary cutaneous marginal zone lymphoma** showed no significant differences in the distribution of CD1a+ cells, although an interstitial distribution of these cells (rather than a peripheral concentration of cells) had been said to favor pseudolymphomatous folliculitis. The authors of this study concluded that the most helpful morphological feature in diagnosing pseudolymphomatous folliculitis is the finding of "activated" follicular units, which display deformed outlines and blurred epithelial borders (see Chapter 42, Pseudolymphomatous Folliculitis).

An approach to the interpretation of skin biopsies

2

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. These 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 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 4) 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. 2.1**). 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 Chapter 4, Introduction). 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, causes, 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. 2.2**). It is a feature of the various types of poikiloderma (see Chapter 4, Poikilodermas).

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

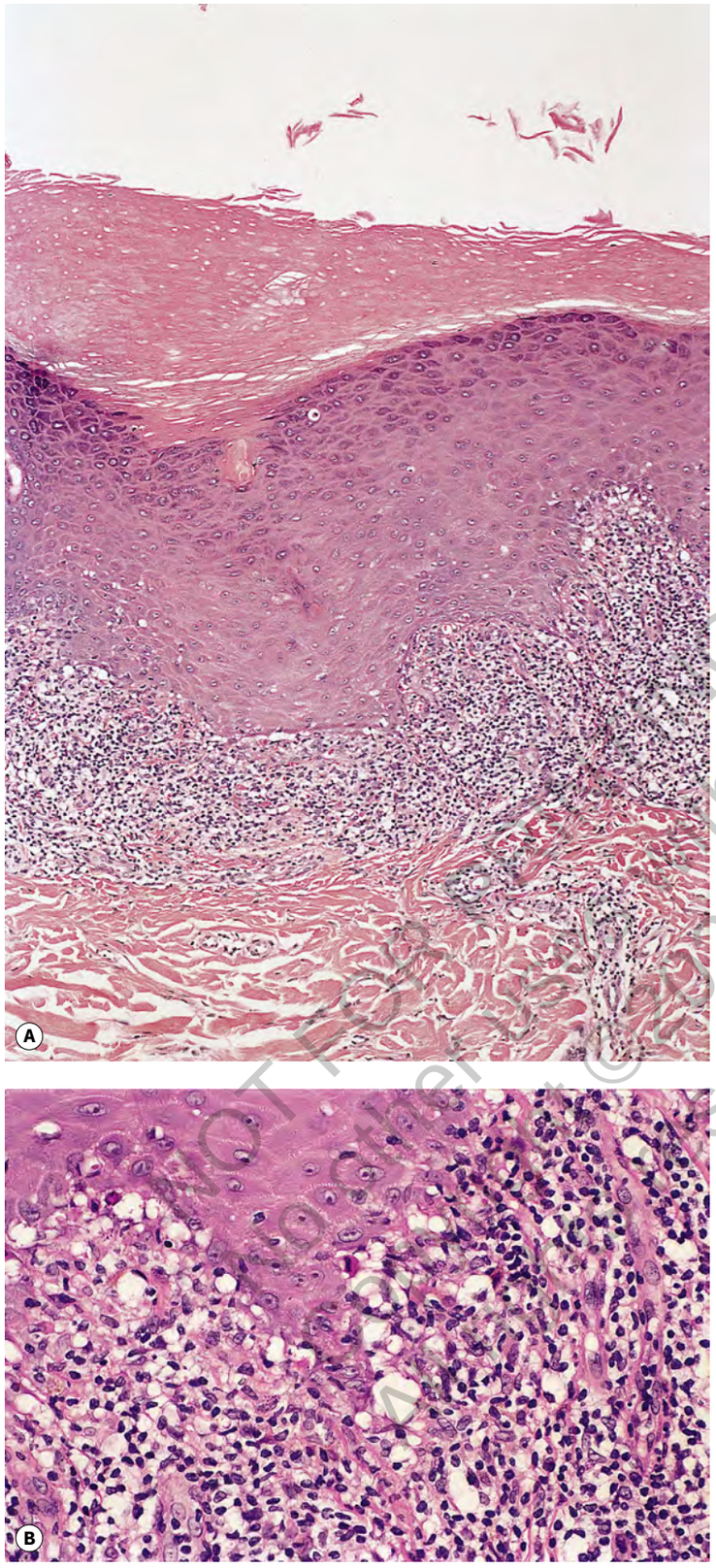

Fig. 2.1 The lichenoid reaction pattern. (A) There are shrunken keratinocytes with pyknotic nuclear remnants (Civatte bodies) in the basal layer. These cells are undergoing death by apoptosis. **(B)** There is also focal vacuolar change. (H&E)

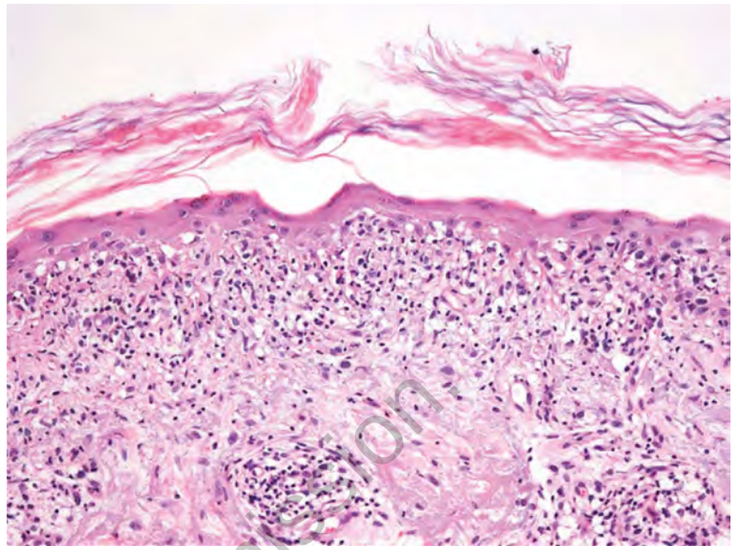

Fig. 2.2 The poikilodermatous variant of the lichenoid reaction pattern. It is characterized by vacuolar change of the basal layer of the epidermis, epidermal atrophy, and dilatation of vessels in the papillary dermis. (H&E)

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 2.1**.

THE PSORIASIFORM REACTION PATTERN

From a morphological standpoint, the psoriasiform tissue reaction (see Chapter 5) is defined as *epidermal hyperplasia in which there is elongation of the rete ridges, usually in a regular manner* (**Fig. 2.3**).

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

Table 2.1 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 amyloidosis
Vitiligo
Lichenoid tattoo reaction

*These diseases may have a true interface pattern.
ID, Interface dermatitis.

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.

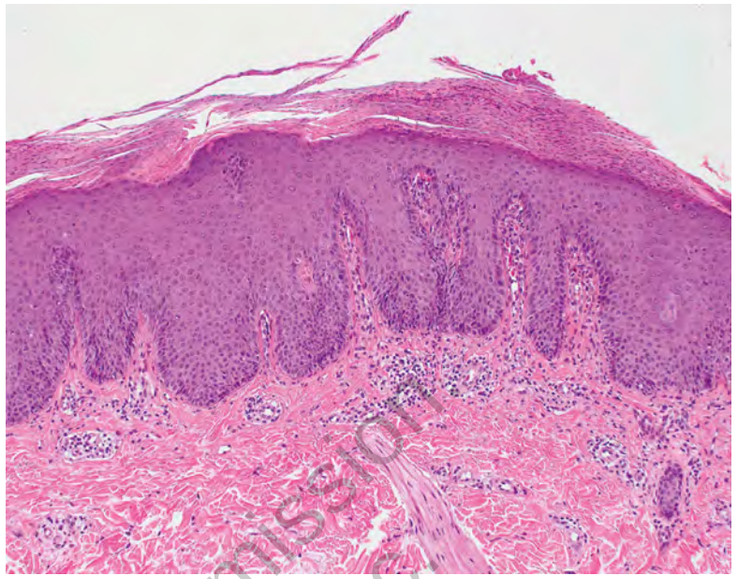

Fig. 2.3 The psoriasiform reaction pattern showing epidermal hyperplasia with regular elongation of the rete processes. In this example of psoriasis, there is hyperkeratosis with parakeratosis, containing numerous neutrophils. (H&E)

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

Diseases showing the psoriasiform reaction pattern are listed in **Table 2.2**.

THE SPONGIOTIC REACTION PATTERN

The spongiotic reaction pattern (see Chapter 6) is characterized by *intraepidermal intercellular edema (spongiosis)*. It is recognized by the presence of widened intercellular spaces between keratinocytes, with elongation of the intercellular bridges (**Fig. 2.4**). Spongiosis may vary from microscopic foci to grossly visible vesicles. This reaction pattern was 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. 2.5**). 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)
2. *Eosinophilic spongiosis* (where there are numerous eosinophils within foci of spongiosis)

Table 2.2 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

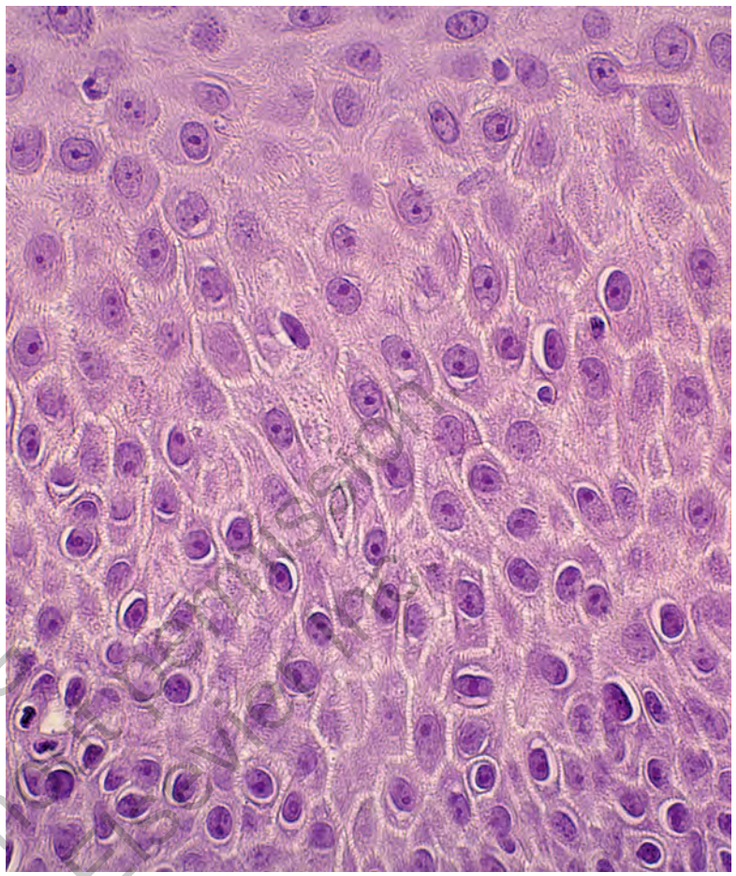

Fig. 2.4 The spongiotic reaction pattern. There is mild intercellular edema with elongation of the intercellular bridges. (H&E)

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 2.3**.

A seventh pattern, which is really a variant of haphazard spongiosis, combines epidermal spongiosis with subepidermal edema (**Fig. 2.6**), which can vary from mild to severe, even forming subepidermal blisters. Its causes are listed in **Table 2.4**.

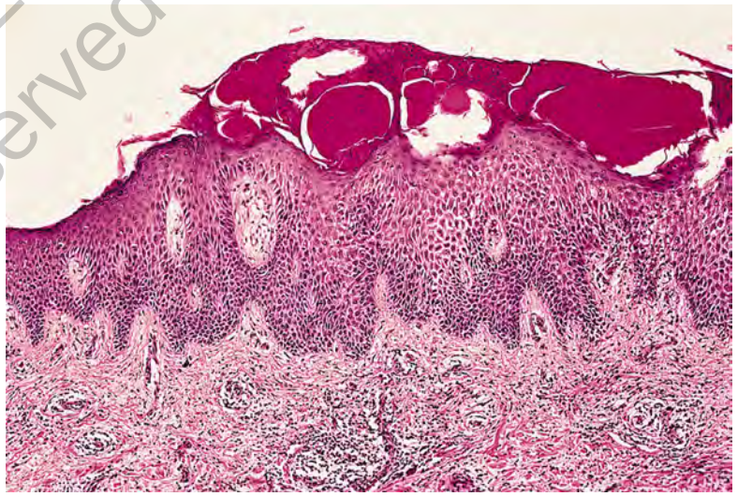

Fig. 2.5 The spongiotic reaction pattern in a lesion of some duration. Psoriasiform hyperplasia coexists with spongiosis. (H&E)

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 7). 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

Table 2.3 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

GVHD, Graft-versus-host disease; *ID*, interface dermatitis; *IgA*, immunoglobulin A; *PUPPP*, pruritic urticarial papules and plaques of pregnancy.

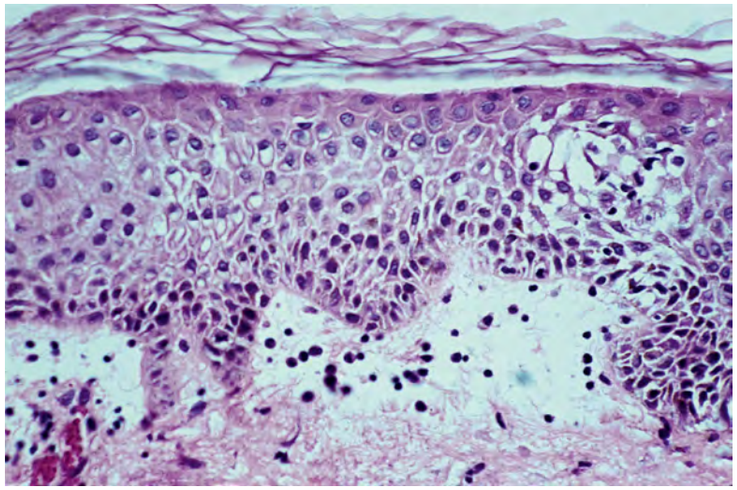

Fig. 2.6 Epidermal spongiosis combined with subepidermal edema. This combination characterizes a certain group of diseases. (H&E)

Table 2.4 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)

ID, Interface dermatitis; *PUPPP,* pruritic urticarial papules and plaques of pregnancy.

practice, the subepidermal blisters are subdivided on the basis of the *inflammatory cell infiltrate within the dermis* (**Fig. 2.7**). Knowledge of immunofluorescence findings is often helpful in categorizing the subepidermal blistering diseases.

Table 2.5 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.

THE GRANULOMATOUS REACTION PATTERN

This group of diseases (see Chapter 8) is characterized by the presence of *chronic granulomatous inflammation*—that is, localized collections of epithelioid cells usually admixed with giant cells, lymphocytes, plasma cells,

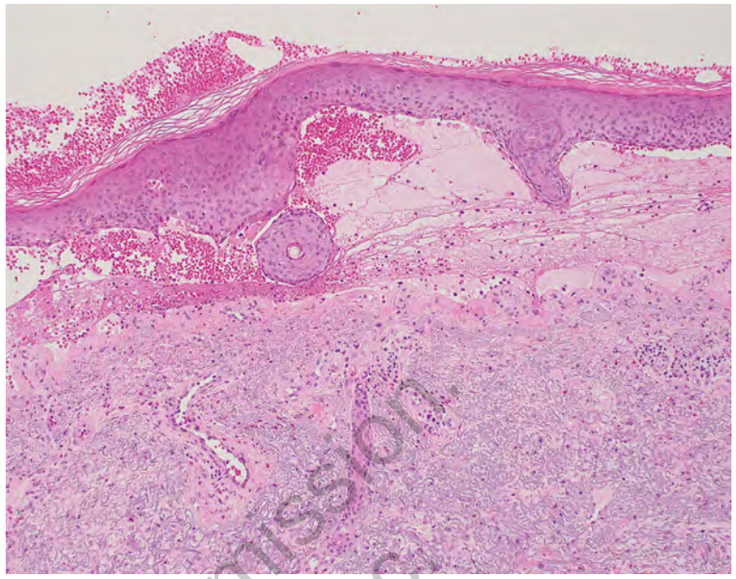

Fig. 2.7 The vesiculobullous reaction pattern. In this case, the blister is subepidermal, so further characterization of it requires an assessment of the inflammatory cell infiltrate within the dermis—in this case, eosinophils. (H&E)

fibroblasts, and nonepithelioid macrophages (**Fig. 2.8**). Five histological types of granulomas 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.

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.

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)

Table 2.5 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.
IgA, Immunoglobulin A; *PUVA,* Psoralen-UV-A.

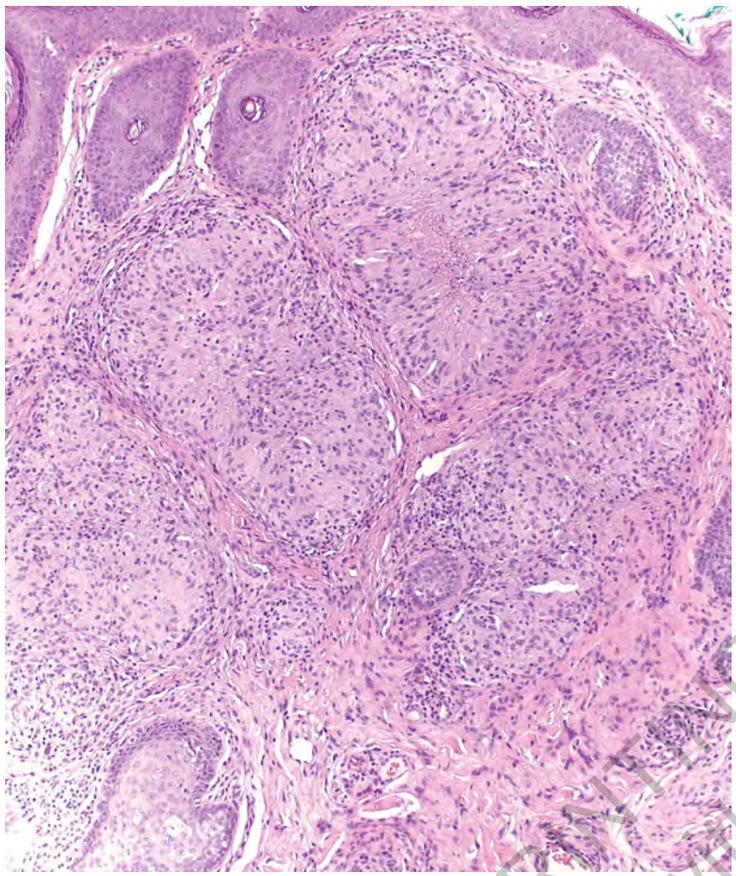

Fig. 2.8 The granulomatous reaction pattern. Tuberculoid granulomas are present in the dermis. (H&E)

or by culture may be necessary to make a specific diagnosis. Organisms are usually scanty in granulomas associated with 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 2.6** 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 9) 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. 2.9**). Some dermatopathologists insist on the presence of fibrin within the vessel wall before accepting 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 that 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 acute vasculitis may progress with time to a chronic stage. Fibrin is rarely present in these late lesions.

Other categories of vascular disease include noninflammatory 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 also included because they share some morphological features with the acute vasculitides.

The diseases showing the vasculopathic reaction pattern are listed in **Table 2.7.**

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 commonly encountered include lichenoid and spongiotic, lichenoid and granulomatous, and lichenoid and vasculopathic.

The various diseases that show these dual patterns are listed in **Table 2.8.**

MINOR TISSUE REACTION PATTERNS

Minor tissue reaction patterns represents 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

Table 2.6 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	

ID, Interface dermatitis.

Chapter 10. Angiofibromas are included with tumors of fibrous tissue in Chapter 35, whereas eosinophilic cellulitis is discussed with the cutaneous infiltrates in Chapter 41. Transepithelial elimination is a process that may occur as a secondary event in a wide range of skin diseases. It will be 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. 2.10**). 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.

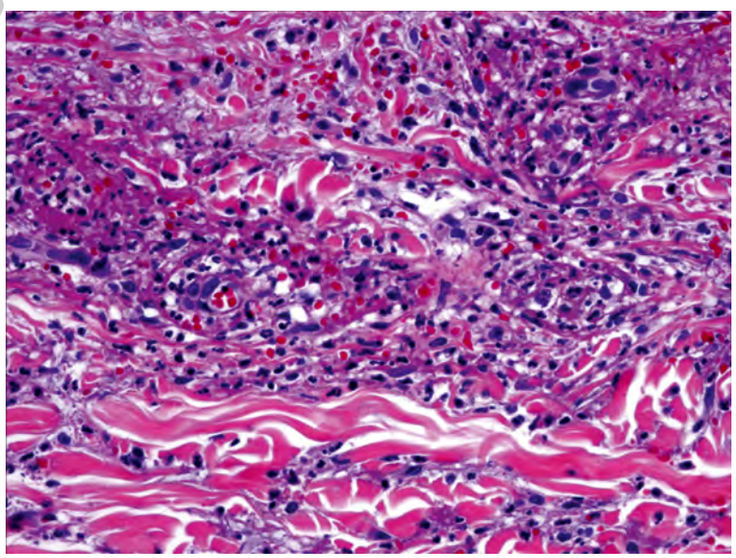

Fig. 2.9 Acute vasculitis. Neutrophils are present in the walls of vessels, with leukocytoclasis and erythrocyte extravasation. (H&E)

Table 2.7 Diseases showing the vasculopathic reaction pattern

Noninflammatory 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	

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *PUPPP,* pruritic urticarial papules and plaques of pregnancy; *TRAPS,* tumor necrosis factor receptor–associated periodic syndrome.

Table 2.8 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

ACE, Angiotensin converting enzyme; *GVHD*, Graft-versus-host disease; *ID*, interface dermatitis.

ACANTHOLYTIC DYSKERATOSIS

Acantholytic dyskeratosis is characterized by *suprabasilar clefting with acantholytic and dyskeratotic cells at all levels of the epidermis* (see Chapter 10, Acantholytic Dyskeratosis) (**Fig. 2.11**). 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).

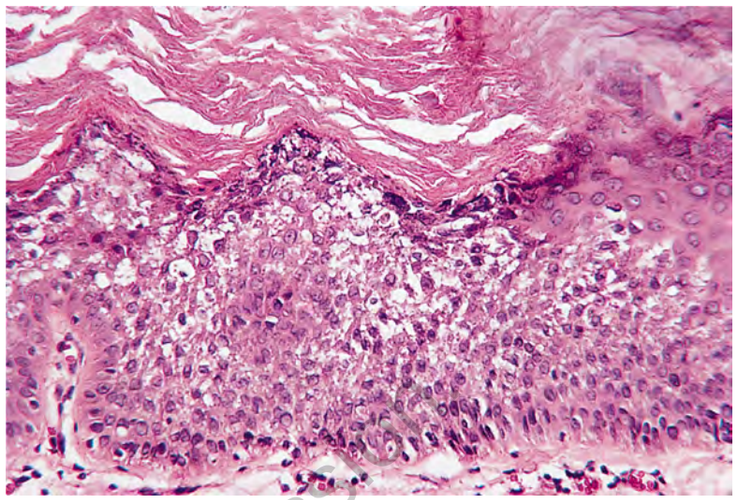

Fig. 2.10 Epidermolytic hyperkeratosis characterized by granular and vacuolar degeneration of the upper layers of the epidermis and overlying hyperkeratosis. (H&E)

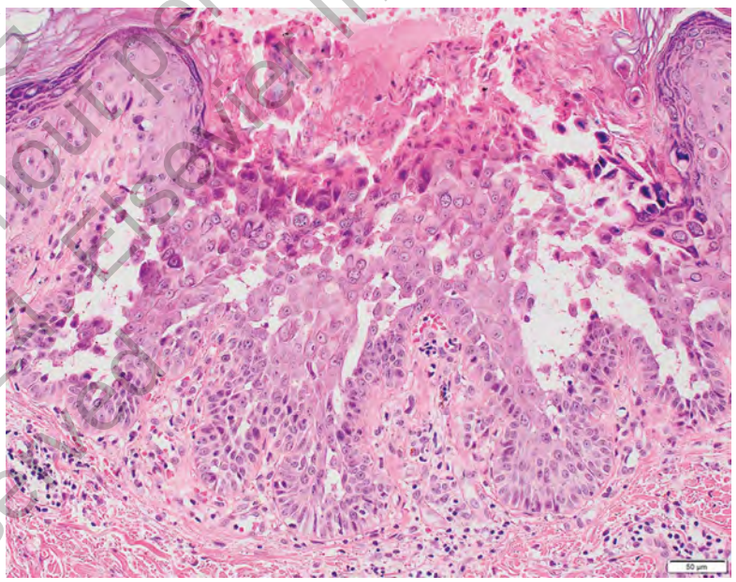

Fig. 2.11 Acantholytic dyskeratosis including suprabasilar clefting and numerous dyskeratotic cells in the overlying epidermis. (H&E)

CORNOID LAMELLATION

Cornoid lamellation (**Fig. 2.12**) 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 Chapter 10, Cornoid Lamellation). Although cornoid lamellation is 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.

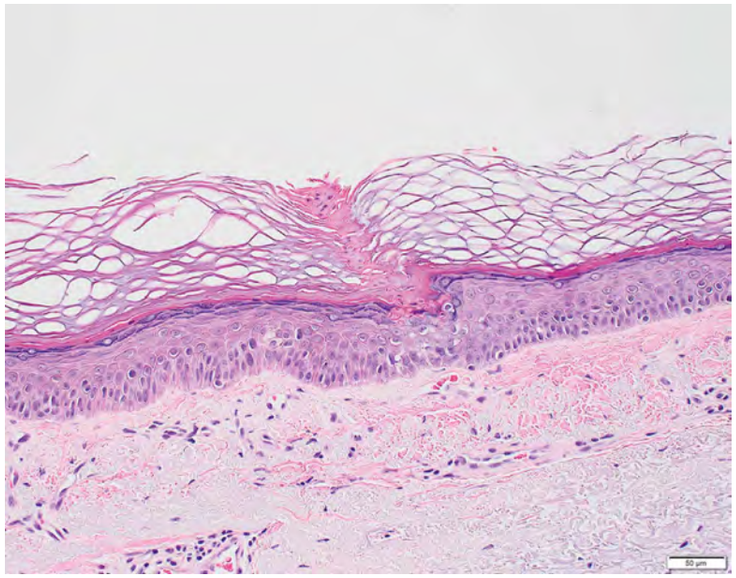

Fig. 2.12 A cornoid lamella in porokeratosis. A thin column of parakeratotic cells overlies a narrow zone in which the granular layer is disrupted. (H&E)

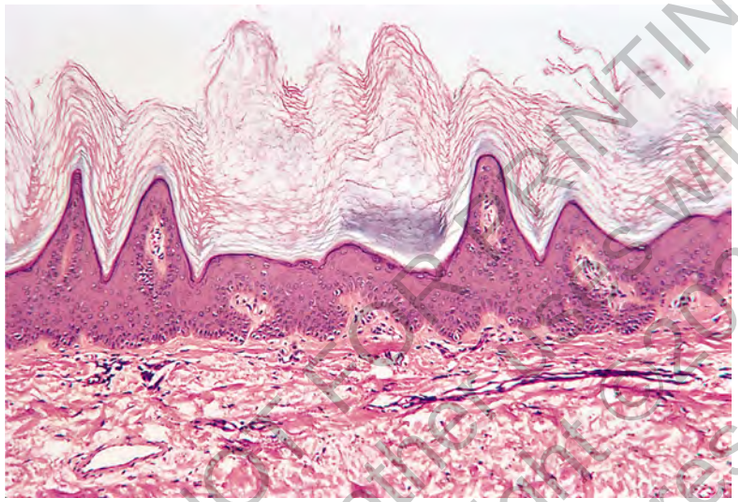

Fig. 2.13 Papillomatosis ("church-spiring"). This is acrokeratosis verruciformis. (H&E)

PAPILLOMATOSIS ("CHURCH-SPIRING")

Papillomatosis refers to the presence of undulations or projections of the epidermal surface (**Fig. 2.13**). 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 2.9**.

Table 2.9 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

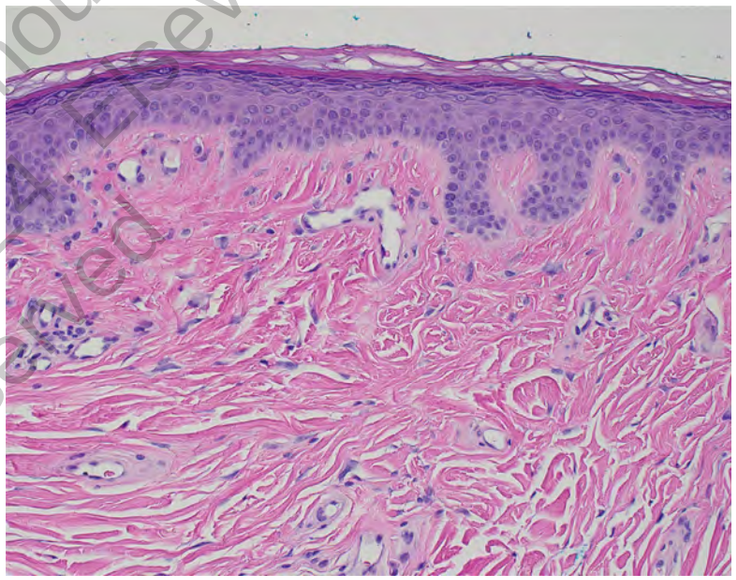

Fig. 2.14 Angiofibroma. There are dilated vessels with intervening fibrosis and stellate cells. (H&E)

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 Chapter 35, Acral Angiofibromas). The fibrous tissue usually contains stellate cells (**Fig. 2.14**). The conditions showing this reaction pattern are listed in **Table 2.10**.

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. 2.15**). "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

Table 2.10 Conditions showing an angiofibromatous pattern

Adenoma sebaceum (tuberous sclerosis)
Angiofibromas in syndromes—multiple endocrine neoplasia 1 (MEN1), neurofibromatosis
Subungual and periungual fibroma
Acquired acral fibrokeratoma
Fibrous papule of the nose (and face)
Pearly penile papules
Familial myxovascular fibromas

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 Chapter 41, Wells' Syndrome). 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.

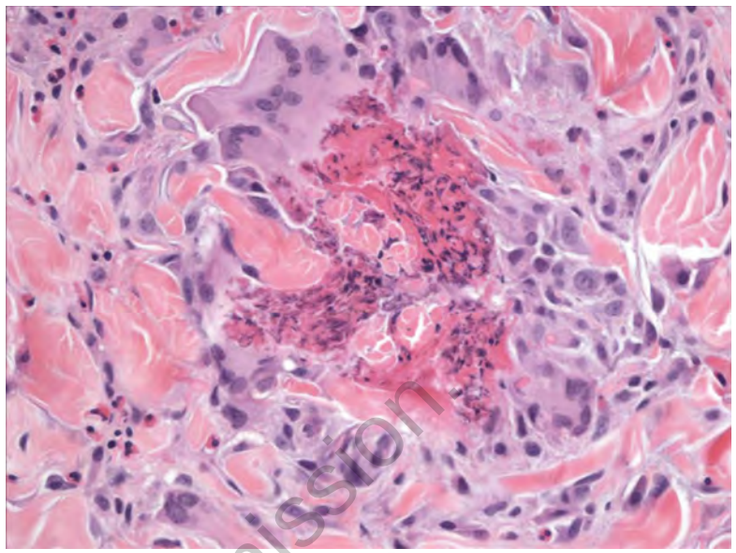

Fig. 2.15 Eosinophilic cellulitis with flame figure. In this case, the flame figure is surrounded by granulomatous inflammation. (H&E)

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 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. 2.16**). 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.[3–19] The various disorders (also known as "perforating disorders") that may show transepithelial elimination are listed in **Table 2.11**.

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.[20] This process was probably an artifact of tissue sectioning.

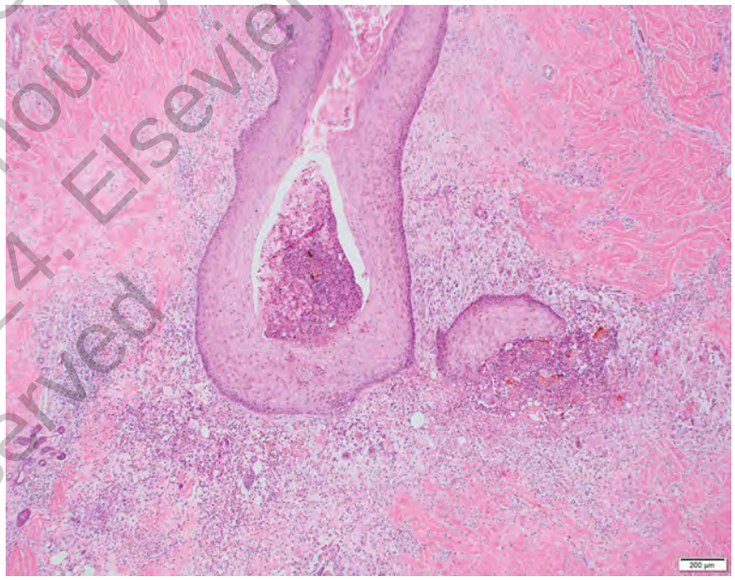

Fig. 2.16 Transepithelial elimination of cellular debris, pigment, and degenerated connective tissue is occurring through a follicular unit. (H&E)

PATTERNS OF INFLAMMATION

Five 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, eccrine and perieccrine infiltrates, 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

Table 2.11 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
Postcryotherapy injury
Cutaneous tumors
Lepra bacilli
Cryocrystalglobulinemia

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
- 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. 2.17**). 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).

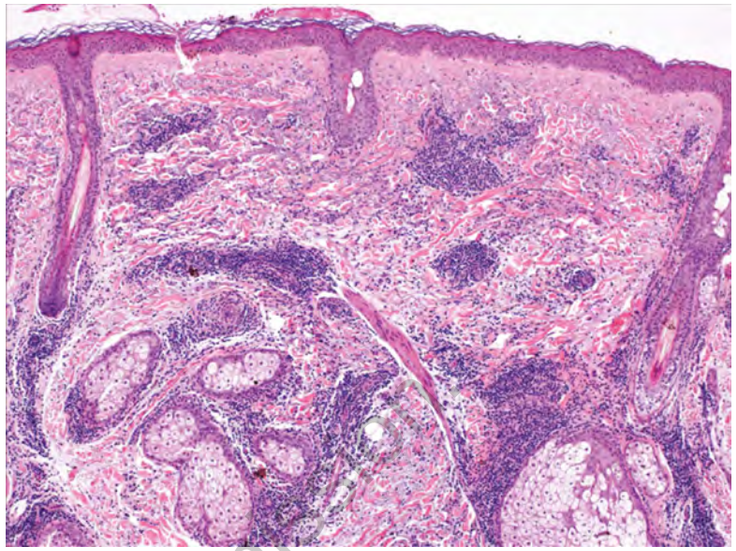

Fig. 2.17 There is a superficial and deep, perivascular and periadnexal infiltrate of lymphocytes. This case, originally diagnosed as lymphocytic infiltrate of Jessner, would now be referred to as tumid lupus erythematosus. (H&E)

This list is obviously incomplete, but it covers most of the important diseases having this pattern of inflammation. For example, 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. 2.18**). 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 caused by an infectious agent, the follicle may be inflamed throughout its entire length. The folliculitides are discussed in further detail in Chapter 16.

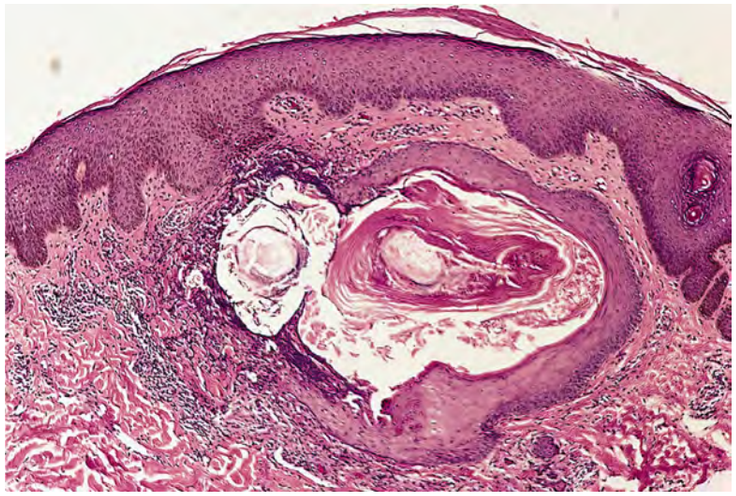

Fig. 2.18 The acute folliculitis has ruptured with extension of the inflammatory infiltrate into the adjacent dermis. (H&E)

Infectious agents are an important cause of folliculitis and perifolliculitis, and diseases showing this pattern of inflammation are sometimes subclassified into "infective" and "noninfective" 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 noninfective 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 noninfective 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 overlapping features. Further subdivision into infective and noninfective 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.

ECCRINE AND PERIECCRINE INFILTRATES

Miliaria is associated with superficial vesiculation, spongiosis, and inflammation involving intraepidermal portions of the eccrine sweat duct; miliaria profunda can also involve the straight, superficial dermal portions of the eccrine duct. Lymphocytic inflammation involving eccrine sweat ducts and glands sometimes occurs in association with folliculitis and perifolliculitis, the classic example being cutaneous *lupus erythematosus*. Perieccrine lymphocytic infiltrates are also seen in *lichen striatus*, with involvement of ductal and secretory portions of the glands, and a lichenoid infiltrate focused on the acrosyringium occurs in *keratosis lichenoides chronica* and accounts for the term *lichen planoporitis* applied to a subset of cases. Dense lymphocytic infiltrates involving hyperplastic sweat ducts occur in *syringolymphoid hyperplasia*, which often represents syringotropic cutaneous T-cell lymphoma and can also coexist with folliculotropic T-cell lymphoma. The rare *lymphocytic autoimmune hidradenitis* is a manifestation of Sjögren's syndrome. *Neutrophilic eccrine hidradenitis* is most closely associated with chemotherapy for leukemia but has also occurred in leukemia unassociated with chemotherapy, with other cancers and therapeutic agents, with Behcet's disease, and rarely with infection. *Palmoplantar eccrine hidradenitis*, particularly occurring in children, shows dense neutrophilic infiltrates involving primarily eccrine ducts with partial sparing of secretory elements.

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 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. 2.19**). The various panniculitides are listed in **Table 2.12**. They are discussed further in Chapter 18.

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The complete reference list can be found online at eBooks.Health.Elsevier.com.

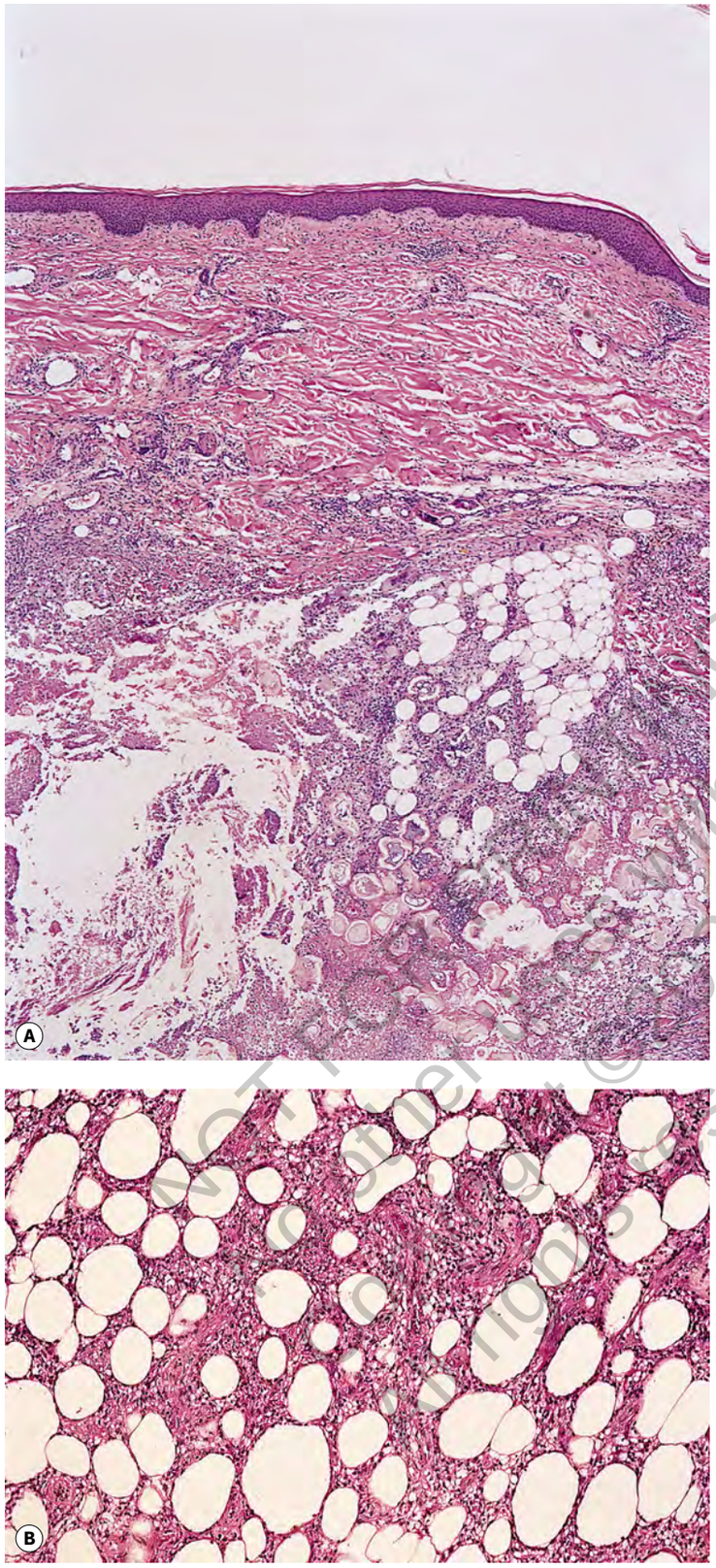

Fig. 2.19 **(A)** Panniculitis of lobular type is present in a case of pancreatic panniculitis. **(B)** Another example of lobular panniculitis in a patient with erythema induratum—nodular vasculitis. (H&E)

Table 2.12 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
Poststeroid panniculitis
Lipodystrophy syndromes
Membranous lipodystrophy
Lipodermatosclerosis
Factitial panniculitis
Traumatic fat necrosis
Infective panniculitis
Noninfective neutrophilic panniculitis
Eosinophilic panniculitis
Panniculitis secondary to large vessel vasculitis
Cutaneous polyarteritis nodosa
Superficial migratory thrombophlebitis

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