SKIN DISEASES OF THE DOG AND CAT

Clinical and Histopathologic Diagnosis

Second Edition
First published as Veterinary Dermatopathology

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Preface and acknowledgements

Much has occurred in the world of veterinary dermatology and veterinary dermatopathology since the publication of *Veterinary Dermatopathology: A Macroscopic and Microscopic Evaluation of Canine and Feline Skin Disease* in 1992. Since then, four additional world congresses devoted to our specialty discipline, many textbooks, an exponential explosion of publications in refereed journals, and international listservs have added substantially to the body of knowledge.

We elected to change the name of this book to *Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis* to more accurately reflect the scope of the content and the goals of this text. Pathogenesis, clinical and histopathologic description, and clinical and histopathologic differential diagnosis have all been expanded to reflect the growth of our discipline. This book sees the addition of over three dozen new inflammatory diseases alone, as well as numerous neoplastic entities. We also introduce our new co-author, Verena Affolter, the principal author of the chapters describing mesenchymal neoplasia.

As in the first book, inflammatory diseases are grouped by histologic pattern. However, since histopathologic classification usually reflects changes observed clinically, clinically relevant groupings often result. The authors have striven to present information in a diagnostically relevant way for clinicians and pathologists alike. Etiopathogenesis (where known), clinical features, and the histopathologic lesions are described for each disease; methods of optimal biopsy are included for inflammatory diseases as well.

Classification systems for skin tumors were established early in veterinary pathology with sporadic additions of newer entities over the years. Standardized international nomenclature was adopted over 25 years ago, and the long-awaited, revised World Health Organization classifications were published in 1998. The authors are gratified that these new WHO fascicles incorporated many of the changes in terminology proposed in the first edition of *Veterinary Dermatopathology*. New information has warranted the extensive revision and expansion of the chapters covering neoplastic diseases, including the addition of immunohistochemical diagnosis. Much of the enhanced precision with which neoplastic lesions are categorized as to cell of origin or path of differentiation reflects the application of immunohistochemistry for cell markers. This is especially true for single cytokeratin markers and hematopoietic cell markers, many of which have become readily available for use on formalin-fixed tissue only in the past few years. The failure of many immunohistochemical reagents developed for use in humans to stain specimens from other animal species continues to be a source of frustration; the authors are hopeful that the development of additional clones or animal-specific clones will allow continued advances. This new book also expands relevant information on analogous tumors from the human dermatopathology literature. The authors believe that comparative dermatopathology is an invaluable tool for the understanding of pathogenesis, the recognition of new diseases, and the advance of research.

It is well to remember that nomenclature is man-made and diseases are biologic aberrations; there will always be lesions that refuse to fit neatly into any given classification system. Large gaps in our knowledge certainly still exist. It is precisely those gaps that the authors hope will serve as inspiration for current and future colleagues to engage in continued critical thinking, clinical studies, and research in the field of dermatology and dermatopathology.

We owe David Lloyd a special tribute as we consider him to be the initial force behind this book. His constant encouragement and early contact with Blackwell Publishing helped initiate the launch of this project. The authors thank Danny Scott, Bill Miller, and Craig Griffin for providing the 6th edition of *Muller & Kirk's Small Animal Dermatology*. Our task was made much easier by having available such a complete and well-referenced textbook. The authors also thank Michael Goldschmidt and Fran Shofer for providing numeric data in such an easily accessible format in *Skin Tumors of the Dog & Cat*.

As for the first edition, we thank M. Donald McGavin for his role as photomicrographic mentor. His talents are

unequaled and we can hope to have achieved only some semblance of his proficiency in these pages.

We are indebted to the dermatologists and pathologists from around the world who gave generously of their clinical photographs, tissue blocks, and knowledge on our behalf. We offer special thanks to Thierry Olivry, Jan Declercq, and Ann Hargis for their unselfish gifts of time, case material, and opinions. Thierry Olivry contributed substantially as a reviewer of Chapter 2 in his capacity as expert in the field of autoimmune subepidermal bullous diseases, and Jan Declercq provided excellent clinical photographs for many diseases as well as blocks and slides of uncommon diseases for histopathologic study. We would be remiss not to single out Zeineb Alhaidari, Kim Boyanowski, Didier Carlotti, Jacques Fontaine, Amy Grooters, Richard Malik, Peter Moore, Claudia Nett, Manon Paradis, Helen Power, Michelle Rosenbaum, Danny Scott, Sheila Torres, Carlo Vitale, and Stephen White for their invaluable assistance. In addition, we thank our many other colleagues, too numerous to mention individually, who responded graciously via the VetDerm listserv to our global plea for material about uncommon, rare, or regional skin diseases.

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Contents

SECTION ONE: INFLAMMATORY, DYSPLASTIC, AND DEGENERATIVE DISEASES

PART I DISEASES OF THE EPIDERMIS 3

1 Pustular Diseases of the Epidermis 4
Impetigo 4
Superficial spreading pyoderma 6
Candidiasis 9
Superficial pustular dermatophytosis 11
Pemphigus foliaceus 13
Pemphigus erythematosus 18
Subcorneal pustular dermatosis 19
Sterile pustular erythroderma of Miniature Schnauzers 20
Superficial pustular drug reactions 23

2 Bullous and Acantholytic Diseases of the Epidermis and the Dermal–Epidermal Junction 27
Bullous pemphigoid 27
Mucous membrane pemphigoid 30
Pemphigus vulgaris 32
Paraneoplastic pemphigus 36
Hereditary epidermolysis bullosa 38
Epidermolysis bullosa acquisita 40
Canine Darier's disease 43
Linear IgA disease 45

3 Interface Diseases of the Dermal–Epidermal Junction 49
Ischemic dermatopathy/canine dermatomyositis 49
Discoid lupus erythematosus 52
Systemic lupus erythematosus 55
Pemphigus erythematosus 57
Exfoliative cutaneous lupus erythematosus of the German Shorthaired Pointer 59
Vesicular cutaneous lupus erythematosus of the Shetland Sheepdog and Collie 61
Erythema ab igne 63
Erythema multiforme 65
Feline thymoma-associated exfoliative dermatitis 68
Lupoid onychitis 70

4 Necrotizing Diseases of the Epidermis 75
Erythema multiforme 75
Feline thymoma-associated exfoliative dermatitis 78
Proliferative necrotizing otitis of kittens 79
Toxic epidermal necrolysis 80
Toxic shock syndrome of dogs 84
Superficial necrolytic dermatitis 86
Generic dog food dermatosis 91
Split pawpad disease 92
Burns 94
Irritant contact dermatitis 98

5 Spongiotic and Vesicular Diseases of the Epidermis 105
Allergic contact dermatitis 105
Feline eosinophilic plaque 109
Psoriasiform dermatitis of the pawpads 111
Facial dermatitis of Persian and Himalayan cats 112

6 Ulcerative and Crusting Diseases of the Epidermis 116
Pyotraumatic dermatitis 116
Feline allergic miliary dermatitis 118
Feline eosinophilic plaque 121
Feline mosquito bite hypersensitivity 122
Feline herpesvirus ulcerative dermatitis 124
Feline cowpox virus infection 127
Feline indolent ulcer 128
Feline idiopathic ulcerative dermatosis 130
Canine pyoderma gangrenosum 132

7 Hyperplastic Diseases of the Epidermis 136
Chronic hyperplastic dermatitis 136
Fibropruritic nodules 138
Acral lick dermatitis 140
Malassezia dermatitis 142

Hyperplastic dermatosis of the West Highland White Terrier 146
Actinic keratosis 148
Acanthosis nigricans of Dachshunds 151
Psoriasiform-lichenoid dermatosis 152
Lichenoid keratosis 154
Inflamed linear epidermal nevus 155
Giant cell dermatosis in FeLV-positive cats 157

8 Diseases with Abnormal Cornification 161
Primary seborrhea and seborrheic dermatitis 161
Vitamin A-responsive dermatosis 165
Canine ear margin seborrhea 167
Nasodigital hyperkeratosis 169
Nasal parakeratosis of Labrador Retrievers 170
Congenital follicular parakeratosis 172
Ichthyosis 174
Familial pawpad hyperkeratosis 179
Schnauzer comedo syndrome 181
Actinic comedones 183
Callus 184
Sebaceous adenitis 186
Zinc-responsive dermatosis 188
Superficial necrolytic dermatitis 191
Inflamed linear epidermal nevus 191
Acrodermatitis of Bull Terriers 193

PART II DISEASES OF THE DERMIS 199

9 Perivascular Diseases of the Dermis 200
Superficial spreading pyoderma 200
Atopic dermatitis 200
Food allergy 206
Canine flea allergy dermatitis 208
Feline allergic miliary dermatitis 211
Urticarial allergic eruption 212
Allergic contact dermatitis 214
Canine sarcoptic acariasis 216
Feline notoedric acariasis 219
Cheyletiellosis 220
Feline superficial demodicosis 222
Cutaneous microfilariasis 225
Hookworm dermatitis 228
Cutaneous anatrichosomiasis 229
Vitiligo 231

10 Vascular Diseases of the Dermis 238
Septic vasculitis 238
Urticaria and angioedema 239
Telangiectasia, phlebectasia, and cutaneous flushing 241
Cryoglobulinemia and cryofibrinogenemia 243
Neutrophilic immunologic vasculitis 244
Cell poor vasculitis 247
Familial cutaneous vasculopathy of German Shepherd Dogs 250
Vasculopathy of Greyhounds 251
Proliferative thrombovascular necrosis of the pinnae 253
Proliferative arteritis of the nasal philtrum 255
Solar vasculopathy 256

11 Lichenoid Diseases of the Dermis 261
Mucocutaneous pyoderma 261
Discoid lupus erythematosus 263
Pemphigus foliaceus 265
Vogt–Koyanagi–Harada-like syndrome 266
Psoriasiform-lichenoid dermatosis 269
Lichenoid keratosis 271

12 Infectious Nodular and Diffuse Granulomatous and Pyogranulomatous Diseases of the Dermis 272
Actinomycosis and nocardiosis 272
Bacterial pseudomycetoma 275
Feline leprosy syndrome 276
Canine leproid granuloma 281
Opportunistic mycobacterial infection caused by rapidly growing mycobacteria 283
Opportunistic mycobacterial infection caused by *Mycobacterium avium* complex 287
Dermatophytic pseudomycetoma 288
Cutaneous blastomycosis, histoplasmosis, and coccidioidomycosis 291
Cutaneous cryptococcosis 295
Sporotrichosis 298
Cutaneous infections of other opportunistic fungi 301
Cutaneous pythiosis, lagenidiosis, and entomophthoromycosis 303
Cutaneous protothecosis 309
Cutaneous leishmaniasis 312

13 Noninfectious Nodular and Diffuse Granulomatous and Pyogranulomatous Diseases of the Dermis 320
Sterile granuloma and pyogranuloma syndrome 320
Reactive histiocytosis 323
Juvenile sterile granulomatous dermatitis and lymphadenitis 327
Cutaneous xanthoma 330
Canine sarcoidosis 333
Foreign body reactions 334
Palisading granuloma 337

14 Nodular and Diffuse Diseases of the Dermis with Prominent Eosinophils, Neutrophils, or Plasma Cells 342
Arthropod bite reactions 342
Feline mosquito bite hypersensitivity 345
Spider bites 347
Fire ant bites 349

Feline herpesvirus ulcerative dermatitis 351
Feline eosinophilic plaque 352
Feline indolent ulcer 353
Feline eosinophilic granuloma 355
Canine eosinophilic granuloma 358
Canine eosinophilic dermatitis 360
Feline hypereosinophilic syndrome 362
Plasma cell pododermatitis 363
Familial cutaneous vasculopathy of German Shepherd Dogs 364
Canine sterile neutrophilic dermatosis (Sweet's syndrome) 366
Sterile pustular erythroderma of Miniature Schnauzers 369

15 Degenerative, Dysplastic and Depositional Diseases of Dermal Connective Tissue 373
Calcinosis cutis 373
Calcinosis circumscripta 378
Cutaneous mucinosis 380
Cutaneous amyloidosis 383
Ehlers–Danlos syndrome 386
Feline acquired skin fragility syndrome 389
Topical corticosteroid reaction 392
Perforating dermatitis 394
Morphea 396
Cicatricial alopecia 397
Solar elastosis and fibrosis 399

PART III DISEASES OF THE ADNEXA 405

16 Pustular and Nodular Diseases without Adnexal Destruction 406
Superficial bacterial folliculitis 406
Feline dermatophytosis 410
Canine dermatophytosis 413
Pemphigus foliaceus 415
Sterile eosinophilic pustulosis 417

17 Pustular and Nodular Diseases with Adnexal Destruction 420
Deep bacterial folliculitis and furunculosis 420
German Shepherd Dog pyoderma 424
Postgrooming furunculosis 427
Acral lick dermatitis 429
Actinic furunculosis 429
Interdigital furunculosis 431
Callus pyoderma 433
Canine acne 435
Feline acne 437
Kerion 440
Canine demodicosis 442
Feline follicular demodicosis 447
Pelodera dermatitis 449
Eosinophilic furunculosis of the face 450
Sebaceous adenitis 453

18 Mural Diseases of the Hair Follicle 460
Alopecia areata 460
Mural folliculitis due to demodicosis and dermatophytosis 464
Pseudopelade 466
Eosinophilic mucinotic mural folliculitis in dogs 469
Degenerative mucinotic mural folliculitis in cats 472
Granulomatous mural folliculitis in dogs 474
Follicular mucinosis 477

19 Atrophic Diseases of the Adnexa 480
Hypothyroidism 481
Canine hyperglucocorticoidism 484
Feline hyperglucocorticoidism 487
Canine Sertoli cell tumor-associated skin disease 490
Canine female hyperestrogenism 492
Alopecia X 494
Postclipping alopecia 497
Feline paraneoplastic alopecia 498
Acquired pattern alopecia 501
Ischemic dermatopathy/canine dermatomyositis 503
Post-traumatic alopecia 505
Traction alopecia 507
Telogen effluvium 509
Doxorubicin-induced alopecia 510
Excessive physiological shedding 512
Feline psychogenic alopecia 513

20 Dysplastic Diseases of the Adnexa 518
Color dilution alopecia and black hair follicular dysplasia 518
Canine follicular dysplasia 522
Cyclical flank alopecia 525
Congenital hypotrichosis 528
Follicular lipidosis 530
Sebaceous gland hyperplasia 531
Sebaceous gland dysplasia 533

PART IV DISEASES OF THE PANNICULUS 537

21 Diseases of the Panniculus 538
Postrabies vaccination panniculitis 538
Postinjection panniculitis 541
Sterile abscess of repositol injection 542
Traumatic panniculitis 545
Vasculitic panniculitis of thermal burns 547
Idiopathic sterile nodular panniculitis 548
Vasculitic septal panniculitis 551
Feline pansteatitis 552
Metatarsal fistulation of the German Shepherd Dog 553
Pancreatic panniculitis 555

SECTION TWO: NEOPLASMS AND OTHER TUMORS

PART I EPITHELIAL NEOPLASMS AND OTHER TUMORS 561

22 Epidermal Tumors 562
Cutaneous horn of feline pawpad 562
Pawpad keratoma 562
Linear epidermal hamartoma 564
Dermoid cyst 566
Squamous papilloma 567
Viral papilloma 567
Canine pigmented viral plaque 571
Feline viral plaque 574
Actinic keratosis 575
Bowenoid *in situ* carcinoma 578
Squamous cell carcinoma 581
Basal cell carcinoma 589
Basosquamous carcinoma 597

23 Follicular Tumors 604
Follicular hamartoma 605
Fibroadnexal hamartoma 605
Follicular cyst 607
Dilated pore 612
Warty dyskeratoma 612
Trichofolliculoma 614
Trichoepithelioma 616
Infundibular keratinizing acanthoma 619
Tricholemmoma 621
Pilomatricoma 624
Trichoblastoma 625
Malignant trichoepithelioma 634
Malignant pilomatricoma 637

24 Sebaceous Tumors 641
Sebaceous duct cyst 641
Nodular sebaceous hyperplasia 641
Sebaceous hamartoma 643
Sebaceous nevus 643
Sebaceous adenoma 645
Sebaceous epithelioma 647
Sebaceous carcinoma 650
Nodular perianal gland hyperplasia and perianal gland adenoma 655
Perianal gland epithelioma 658
Perianal gland carcinoma 659

25 Sweat Gland Tumors 665
Apocrine cyst 666
Canine apocrine cystomatosis 667
Feline ceruminous cystomatosis 667
Apocrine cystadenoma 668
Apocrine secretory adenoma 670
Apocrine ductular adenoma 672
Apocrine secretory adenocarcinoma 677
Apocrine ductular carcinoma 681
Eccrine carcinoma 689

26 Nailbed Epithelial Tumors 695
Nailbed epithelial inclusion cyst 695
Nailbed inverted squamous papilloma 696
Nailbed keratoacanthoma 698
Nailbed squamous cell carcinoma 700
Nailbed basal cell carcinoma 702
Metastatic pulmonary carcinoma in cats 703

PART II MESENCHYMAL NEOPLASMS AND OTHER TUMORS 709

27 Fibrous Tumors 710
Collagenous hamartoma 710
Canine nodular dermatofibrosis 711
Acrochordon and acrochordonous plaque 713
Dermatofibroma 716
Nodular fasciitis 717
Fibroma 719
Canine keloidal fibroma 721
Fibrosarcoma 722
Myxoma 727
Myxosarcoma 728
Feline sarcoid 730

28 Vascular Tumors 735
Angiomatosis 735
Hemangioma 741
Lymphangiomatosis 748
Hemangiosarcoma 749
Lymphangiosarcoma 753

29 Perivascular Tumors 759
Glomus tumor 759
Hemangiopericytoma 762

30 Lipocytic Tumors 766
Lipomatosis 766
Lipoma 766
Spindle cell lipoma 770
Infiltrative lipoma 771
Liposarcoma 772

31 Smooth Muscle and Skeletal Muscle Tumors 778
Leiomyoma 778
Leiomyosarcoma 779
Canine skeletal muscle hamartoma 782
Rhabdomyosarcoma 783

32 Neural and Perineural Tumors 786
Traumatic neuroma 786
Merkel cell tumor 786
Benign peripheral nerve sheath tumor 789
Malignant peripheral nerve sheath tumor 792

33 Other Mesenchymal Tumors **797**
Vaccine-induced sarcoma 797
Transmissible venereal tumor 800
Ganglion 803
Granular cell tumor 804
Anaplastic sarcoma with giant cells 806

34 Melanocytic Tumors **813**
Lentigo 814
Melanocytoma 815
Melanocytoma–acanthoma 822
Melanoma 825

35 Histiocytic Tumors **837**
Reactive fibrohistiocytic nodule 837
Canine cutaneous histiocytoma 840
Feline progressive dendritic cell histiocytosis 845
Histiocytic sarcoma 848

36 Mast Cell Tumors **853**
Canine mast cell tumor 853
Feline mast cell tumor 858
Cutaneous mastocytosis 861

37 Lymphocytic Tumors **866**
Cutaneous plasmacytoma 866
Cutaneous lymphocytosis 872
Epitheliotropic lymphoma 876
Nonepitheliotropic lymphoma 882
Chronic lymphocytic leukemia with cutaneous lesions 888

Index 895

SECTION ONE

INFLAMMATORY, DYSPLASTIC, AND DEGENERATIVE DISEASES

PART I

Diseases of the Epidermis

Chapter 1

Pustular diseases of the epidermis

Pustular diseases are characterized by the formation of pustules in the epidermis and may range from subcorneal to panepidermal. Pustules result from breakdown in the integrity of the keratinocytes by spongiosis or acantholysis, as well as the accumulation of inflammatory cells that migrate from the underlying dermal vasculature in response to superficial infectious agents or epidermal damage. Pustules may be discrete or poorly defined, and may contain neutrophils, eosinophils, and acantholytic or apoptotic keratinocytes.

IMPETIGO

Clinical features (Figures 1.1 and 1.2)

Impetigo is a common canine bacterial skin disease characterized by superficial nonfollicular pustules. As in other forms of canine pyoderma, *Staphylococcus intermedius* is the primary pathogen. Underlying causes usually are not documented in the most common form of impetigo presenting in prepubescent and pubescent dogs. However, inflammation secondary to fecal debris, urine scalding, hair coat matting, and ectoparasitism may enhance susceptibility; poor environmental hygiene or poor nutrition may be contributory. A much less common bullous form of impetigo, sometimes seen in conjunction with underlying immunosuppression, is most frequently observed in older dogs.

The pathogenesis of impetigo may involve staphylococcal exfoliative toxins, as seen in human bullous impetigo (Prevost et al., 2003). These toxins may also be involved in exfoliative staphylococcal infections such as superficial spreading pyoderma (see p. 6). Exfoliative toxins have recently been identified in dogs with staphylococcal pyoderma (Terauchi et al., 2003). Interestingly, desmoglein 1 is the target of both exfoliative toxins of staphylococci and the antibodies of pemphigus foliaceus in humans (Amagai et al., 2000), which explains morphologic similarities in lesions. Other nonstaphylococcal bacteria such as *Pseudomonas* spp., *Enterobacter* spp., and *Escherichia coli* occasionally may be the primary pathogens in bullous impetigo (Ihrke, 1996).

The primary lesions of canine impetigo in young dogs are nonfollicular pustules. Pustular contents vary from creamy white to yellow. Since intact pustules are fragile and rupture readily, yellowish crusts adherent to mildly erythematous papules may be the predominant clinical feature. Peripheral epidermal collarettes may remain as an additional 'footprint' of pyoderma. Follicular pustules have central protruding hairs in contrast to the interfollicular pustules of impetigo; a hand lens is useful for differentiation. Differentiation is important clinically since impetigo responds more readily to therapy than superficial folliculitis. Occasionally, a small number of follicular pustules (folliculitis) may coexist with impetigo; however, either impetigo or folliculitis will predominate clinically. Impetigo is seen predominantly in the glabrous or sparsely-haired regions of the groin and axillae in young dogs. Partial bilateral symmetry is common. Pruritus, if present, is mild and lesions are non-painful and otherwise asymptomatic.

In bullous impetigo of older dogs due to underlying immune suppression, pustules are larger and range from 5 to 15 mm in diameter. These pustules are flaccid and may span multiple follicles. Pustular contents can vary from white to yellow or even light green. Unusual color in a pustule indicates the likelihood of a less common Gram-negative bacterial infection, and thus warrants bacterial culture. Bullous impetigo is seen most frequently with naturally occurring or iatrogenic hyperglucocorticoidism, but has also been seen in conjunction with diabetes mellitus, hypothyroidism, lymphoid neoplasia, and other debilitating diseases associated with immunosuppression. This subgroup of impetigo usually begins in the glabrous regions of the groin and axillae, but is much more likely to generalize than the impetigo seen in young dogs. Pruritus is uncommon.

Canine impetigo is seen most commonly in prepubescent and pubescent dogs. Impetigo of adult or senile onset is uncommon and suggests underlying disease. Breed or sex predilections have not been noted.

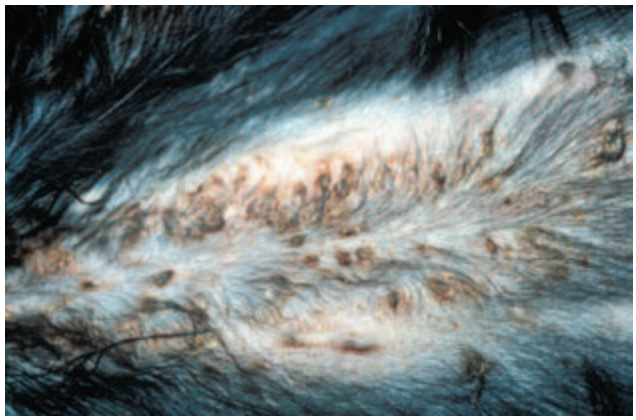

Fig. 1.1 Impetigo of the ventral abdomen of a pubescent dog. Note the multiple crusted papules and the sparse intact pustules.

Fig. 1.2 Bullous impetigo of the ventral abdomen of a Boxer with hyperadrenocorticism. A single large, intact, asymmetrical pustule is surrounded by an erythematous halo. The nipple exhibits calcinosis cutis.

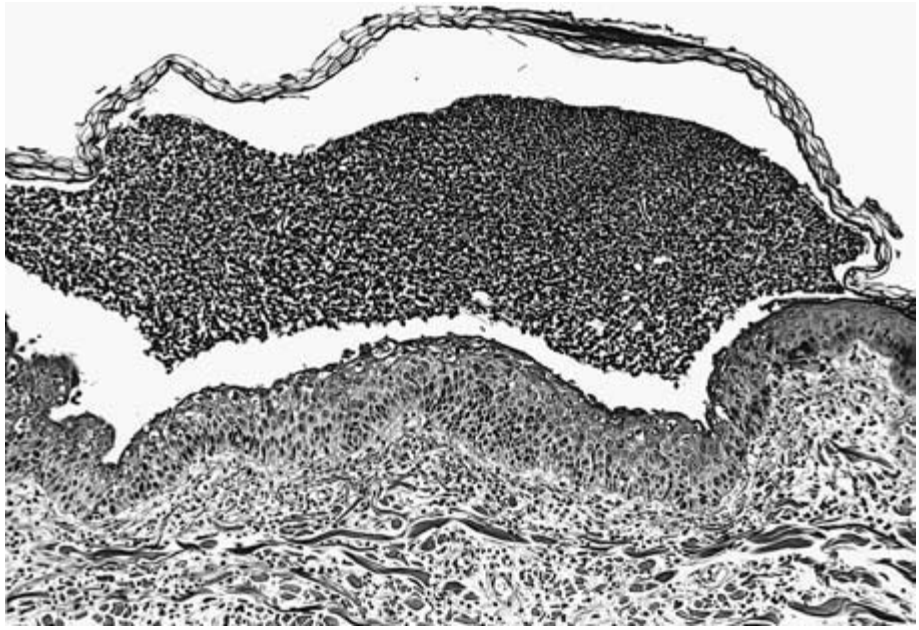

Fig. 1.3 Impetigo in a dog. Note the large, discrete subcorneal pustule with subjacent mild spongiosis.

Clinical differential diagnoses for impetigo of young dogs include early onset flea allergy dermatitis and superficial folliculitis. Pruritus should be evident even with mild flea allergy dermatitis, in contrast to the relatively mild or absent pruritus of impetigo. In folliculitis, the pustules are oriented around hairs and their follicles, rather than between them as in impetigo of young dogs. An uncommon variant of pemphigus foliaceus characterized by intermittent waves of truncal pustules, ranging from 2 to 10 mm in diameter, can mimic bullous impetigo of adult dogs.

Biopsy site selection

Skin biopsy specimens should be obtained from intact pustules, if available. Crusted papules are not ideal as they represent pustules in advanced stages of degeneration.

Histopathology (Figure 1.3)

The typical microscopic lesion is a discrete subcorneal or intragranular pustule that is composed predominantly of neutrophils. Generally, pustules are elevated above the

epidermal surface and are located between hair follicles. In bullous impetigo, broader pustules span one or two hair follicles. Spongiosis often occurs beneath pustules; mild separation of keratinocytes (acantholysis) may be present at the base, or there may be a few intrapustular acantholytic cells. Rarely, there is marked acantholysis, mimicking pemphigus foliaceus (see p. 13). Pustules become crusts as inflammatory cells degenerate, and new stratum corneum often develops at the base of these older lesions. The epidermis is mildly to moderately acanthotic. A bacterial stain often reveals Gram-positive cocci within pustules. Stains are useful diagnostically only if the pustule is intact, as any ruptured pustule may develop secondary bacterial colonization.

The dermis has superficial perivascular to interstitial, mixed inflammation with neutrophils predominating. Mild to moderate dermal edema is common. There may be concurrent folliculitis (see Chapter 16).

The principal differential diagnosis is pemphigus foliaceus, particularly in the case of bullous impetigo, or when acantholysis is prominent. Acantholysis usually is absent or minimal in impetigo and intact pustules reveal bacteria, in contrast to the sterile intact pustules of pemphigus foliaceus. In pemphigus foliaceus, immunoglobulin and frequently C3 may be found in the intercellular spaces of the epidermis and often superficial follicular epithelium with immunofluorescence or immunohistochemical testing (see p. 13). Clinical differentiation may be required if acantholysis is severe and/or if immunohistochemical or immunofluorescence testing is negative or not performed.

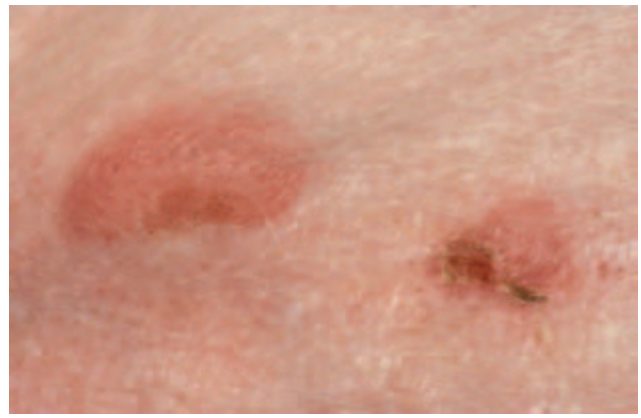

Fig. 1.4 Superficial spreading pyoderma in a dog. Two asymmetrical erythematous macules have slight peripheral collarettes.

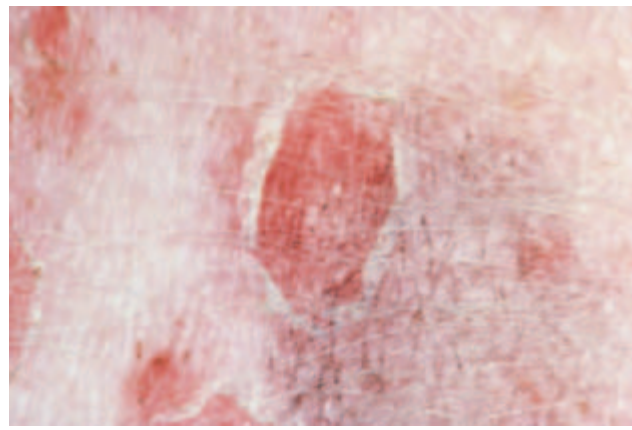

Fig. 1.5 Superficial spreading pyoderma in the glabrous skin of the ventral abdomen of a dog. A large collarette peels peripherally from the border of the erythematous macule.

SUPERFICIAL SPREADING PYODERMA

(Synonym: exfoliative pyoderma)

Clinical features (Figures 1.4 and 1.5)

Superficial spreading pyoderma is a superficial bacterial skin disease seen commonly in the dog and rarely in the cat. *Staphylococcus intermedius* is the primary pathogen, as in other forms of pyoderma. Superficial spreading pyoderma may be seen alone or more commonly in conjunction with superficial bacterial folliculitis (see Chapter 16). Exfoliative toxin has been isolated from strains of *Staphylococcus intermedius* from dogs with pyoderma; the isolated toxin caused exfoliation of the skin of dogs and other species (Terauchi et al., 2003). Similar toxins have also been recovered from pigs with exudative epidermitis, an exfoliative *Staphylococcus hyicus* infection (Tanabe et al., 1996), and are recognized in staphylococcal scalded skin, a severe form of exfoliative staphylococcal infection in humans (Prevost et al., 2003). Superficial spreading pyoderma frequently occurs secondary to other underlying diseases such as canine atopic dermatitis and other allergic skin diseases. In humans, there is a high prevalence of certain staphylococcal superantigens on the skin of patients with atopic dermatitis (Mempel et al., 2003). Recently, staphylococcal superantigens with marked T cell blastogenesis potential have been isolated from *Staphylococcus intermedius* strains obtained from canine pyoderma (Hendricks et al., 2002). The marked inflammation and pruritus seen with canine superficial spreading pyoderma in the setting of atopic dermatitis may be due to superantigen production from inappropriate staphylococcal bacterial colonization in susceptible dogs. Frequent localization of lesions to the glabrous intertriginous regions of the groin and axillae suggests that anatomic factors leading to moisture, heat retention, and frictional micro-trauma may be contributory to bacterial overgrowth and infection (Ihrke, 1996).

The more florid form of superficial spreading pyoderma, seen most commonly in the Shetland Sheepdog, usually is idiopathic; a breed predisposition to coloniza-

tion by exfoliative toxin-producing staphylococci is possible. A cat with chronic feline immunodeficiency virus (FIV) infection presented with antibiotic-responsive lesions that clinically were strikingly similar to canine superficial spreading pyoderma (Radowicz, S., personal communication, 2003).

Erythematous macules enlarge centripetally from tiny transient pustules and create expanding coalescing erythematous rings. At the margins of the expanding macules, superficial keratin layers lift and peel peripherally forming distinctive collarettes with well-demarcated borders. Individual macules commonly achieve diameters of 1 to 2.5 cm. Subtle central crusting may be present. Expanding macules with peripheral collarettes impinge upon each other creating irregular arciform patterns that resemble interconnecting ripples. In well-haired areas, alopecia may occur in ring-like patterns within the confines of the macules. Postinflammatory hyperpigmentation marks the site of previously active lesions. Lesions often are confined to the glabrous skin of the ventrum, but may be more generalized on the trunk. Pruritus is variable and may not correlate with the magnitude of erythema. Superficial bacterial folliculitis may occur in conjunction with superficial spreading pyoderma; one of the two syndromes usually predominates (Ihrke & Gross, 1994) (see Chapter 16). A particularly striking subgroup of combined superficial spreading pyoderma and superficial folliculitis occurs predominantly in Shetland Sheepdogs. In this highly characteristic subgroup, individual coalescing collarettes emanating from sheet-like exfoliation may reach 5 cm in diameter, leading to widespread truncal alopecia.

Age, breed, or sex predilections have not been reported. Shetland Sheepdogs, Border Collies, Australian Shepherds, and Collies may be predisposed to exceptionally florid lesions.

The expanding macules with peripheral coalescing collarettes of superficial spreading pyoderma are distinctive and visually striking. Generalized truncal exfoliation may be seen initially with thyroid hormone supplementation, but is not accompanied by macules, papules, erythema, or collarettes. Clinical differential diagnoses for lesions with peripheral epidermal collarettes include superficial bacterial folliculitis, pemphigus foliaceus, erythema multiforme, and sterile eosinophilic pustulosis. If pruritus and self-trauma are marked, lesions may be considerably less diagnostic and may resemble flea allergy dermatitis or dermatophytosis. History, clinical features, distribution of lesions, and often response to appropriate therapy allow definitive diagnosis.

Biopsy site selection

Specimens for skin biopsy should be obtained from the advancing edge of the collarette. Biopsy of the central region of an erythematous macule is less likely to yield diagnostic results. If pustules are present, they also should be sampled. When performing the skin biopsy, care should be taken not to dislodge the scale present at the margin of the epidermal collarette since this material is most likely to yield a definitive diagnosis.

Histopathology (Figures 1.6 through 1.8)

The microscopic appearance is variable and is highly dependent on the stage and site of lesions obtained for biopsy. Because lesions evolve rapidly in an outward direction, it may be difficult to obtain a diagnostic biopsy.

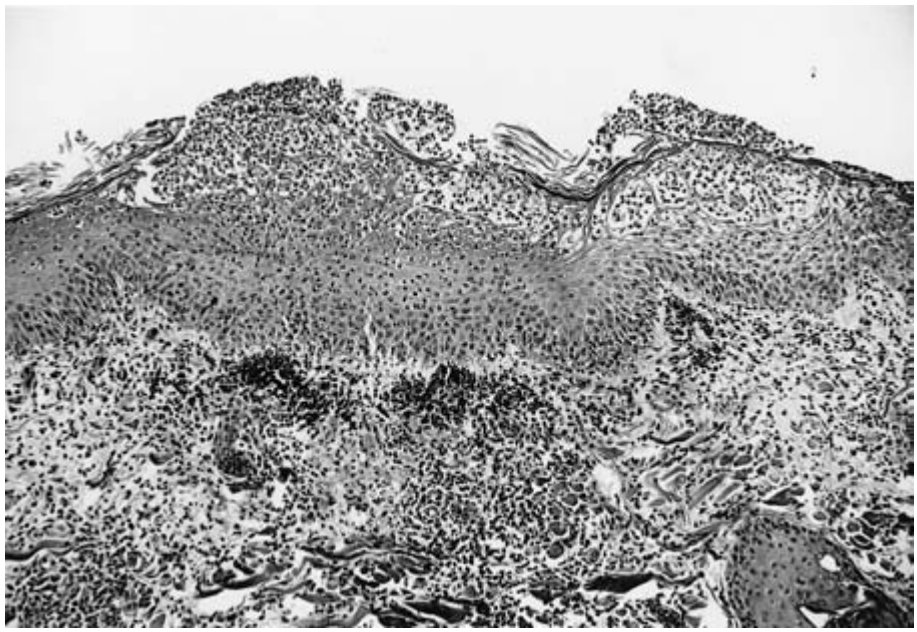

Fig. 1.6 Superficial spreading pyoderma in a dog. A large spongiotic pustule is loosely organized in the superficial epidermis.

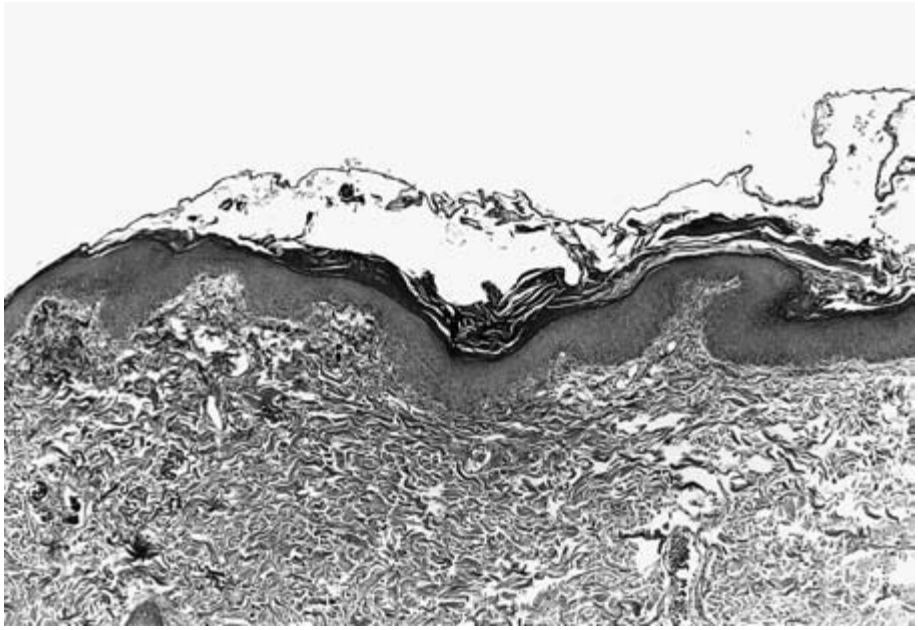

Fig. 1.7 Dunstan's blue line characterized by dark subcorneal deposits of degenerating cellular debris. Note lifting of stratum corneum.

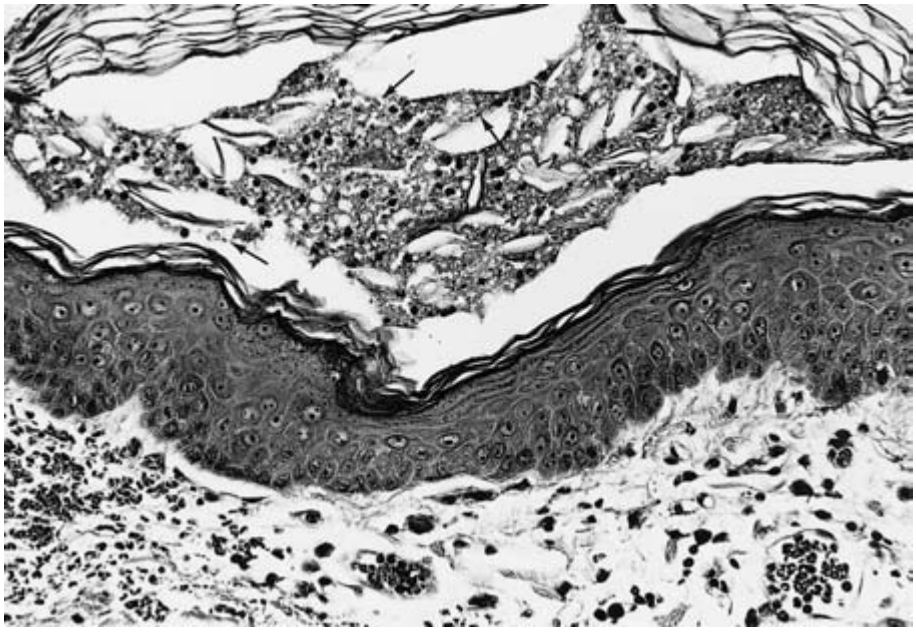

Fig. 1.8 Dunstan's blue line. Degenerating nuclear debris, fragments of keratin, and numerous small cocci (arrows) are intermingled at the advancing edge of a pustule. Note the elevated stratum corneum.

In less optimal specimens, such as those obtained from the center rather than the advancing periphery, epidermal lesions may be absent, making differentiation from chronic dermatitis difficult.

The most characteristic epidermal lesions, obtained from the periphery of an advancing collarette, consist of small, loosely organized and spongiotic, superficial epidermal pustules that rapidly form crusts, accompanied by lifting of the overlying stratum corneum from the epidermal surface. Occasionally, the lifting of the stratum corneum predominates and subjacent epidermal inflammation is subtle; however, a close search usually reveals small crusts within the stratum corneum. The lifted stratum corneum is generally of basketweave appearance.

Gram-positive cocci may be seen within superficial layers of keratin and may be accompanied by granular basophilic cellular debris, collectively referred to as 'Dunstan's blue line'. In cases of minimal inflammation, staphylococci may be distributed in exfoliating keratin in a looser pattern. Lifting of keratin is evident above or just adjacent to the blue line, and this corresponds to the peripheral scaling, or advancing epidermal collarette, seen

clinically. In this respect, lesions of superficial spreading pyoderma resemble those of very early exudative epidermitis, a *Staphylococcus hyicus* infection seen in pigs. Early macroscopic skin lesions of scaling in gnotobiotic pigs correspond to microscopic splitting of the keratin layer and superficial colonization by staphylococci (Lloyd, D.H., Allaker, R.A. & Gross, T.L., unpublished data, 1986). The exfoliative lesions also resemble those of staphylococcal scalded skin in man, from which staphylococcal exotoxins have been isolated, although the canine lesions are clinically not as severe.

The dermis has a superficial perivascular to interstitial admixture of neutrophils, plasma cells, lymphocytes, eosinophils and mast cells. Neutrophils may predominate in some lesions. Mild to moderate dermal edema is common (see Chapter 9).

In the cat with clinical lesions resembling superficial spreading pyoderma (see above) there were large subcorneal pustules that dipped into superficial hair follicles. Mild acantholysis was seen, as in impetigo (see p. 4). The stratum corneum was lifted, but blue line formation was not observed. Dermal inflammation was more severe than observed in dogs, and neutrophils and eosinophils were prominent.

Differential diagnoses include impetigo and impetiginization due to self-trauma from pruritus. Ichthyosis and exfoliation due to thyroid hormone supplementation also must be considered for lesions in which inflammation is subtle. Pustules of superficial spreading pyoderma are rarely as discrete as those of impetigo and do not confine themselves as neatly to the subcorneal space. Lesions of impetiginization found in chronic hyperplastic dermatitis due to allergy (see Chapter 7) are compact neutrophilic crusts, often admixed with parakeratosis or hyperkeratosis, and sometimes accompanied by erosion; frank pustules usually are not seen and lifting of the stratum corneum is not a feature. Lifting of the stratum corneum is a feature of ichthyosis and thyroid hormone supplementation; the lifted keratin is of lamellar rather than basketweave appearance in ichthyosis, but of normal basketweave appearance in thyroid hormone supplementation. Careful searching usually will reveal small crusts within the stratum corneum of lesions of superficial spreading pyoderma, in contrast to the noninflamed stratum corneum of ichthyosis and exfoliation due to thyroid hormone supplementation.

CANDIDIASIS

Clinical features (Figures 1.9 and 1.10)

Candidiasis is a very rare fungal disease reported in dogs and cats that is caused by species of the genus *Candida*. Although *Candida albicans* is the most commonly reported pathogen, many other species have been identified as causative agents in individual cases. Candidiasis usually is seen as an opportunistic infection secondary to underlying immunosuppressive or debilitating systemic disease (Greene & Chandler, 1998). Reported initiators include hyperadrenocorticism, diabetes mellitus, hypothyroidism, cancer, inherited defects of the immune system, and immunosuppressive drug therapy. Disruption of normal barrier function and factors that disturb the normal endogenous microflora may contribute.

Ulcers and erosions are coated with adherent, tenacious, foul-smelling gray exudate. The oral mucosa, mucocutaneous junctions and distal extremities are the most frequently involved sites. Lesions also may be seen in the external ear, perineum, nares, vulva, scrotum, and glabrous intertriginous skin. Pruritus and pain are variable but may be intense. Canine *Candida* pododermatitis may involve single or multiple paws and is characterized by erythema, oozing, pruritus, and pain (Carlotti & Pinn,

Fig. 1.9 Perioral candidiasis in an elderly Poodle with superficial necrolytic dermatitis.

Fig. 1.10 Closer view of Fig 1.9. Dark crusts and tenacious mucoid deposits adhere to erosions and mat the surrounding hair.

1999). In all forms of candidiasis, secondary bacterial invasion may contribute to morbidity, pruritus, and pain.

Sex or breed predilections have not been noted. Candidiasis may be seen more frequently in adult and elderly animals with immunosuppression or debilitation as contributing factors.

Clinical differential diagnoses reflect the site affected. Mucosal and mucocutaneous lesions may mimic autoimmune skin disease (pemphigus vulgaris, bullous pemphigoid, systemic lupus erythematosus), other immunologic diseases (erythema multiforme, epidermolysis bullosa acquisita), epitheliotropic lymphoma (mycosis fungoides), uremic stomatitis, and superficial necrolytic dermatitis. Cutaneous lesions may mimic pyotraumatic dermatitis, and intertriginous candidiasis must be differentiated from bacterial intertrigo. As a further complication, candidiasis may occur secondary to any of the diseases mentioned above, especially if immunosuppression is present. Stained smears from exudate demonstrating blastoconidia and pseudohyphae are a diagnostic aid, but definitive diagnosis cannot be made without biopsy and culture.

Biopsy site selection

Intact crusted lesions should be selected. Care should be taken to leave crusts attached to the specimens. The pathology service should be instructed to include any separated crusts in the slide preparation. Ulcers should not be sampled alone since an intact epidermis or mucosa may be essential for the identification of organisms in tissue.

Histopathology (Figures 1.11 and 1.12)

Microscopic findings consist of moderate to severe, superficial epidermal pustulation, generally composed of neutrophils. Large areas of surface pustulation and serocellular crusting with parakeratosis may be present; discrete small pustules generally are not seen. Subjacent spongiosis is often prominent. Secondary erosion and ulceration are common. Intact epidermis is moderately acanthotic.

Discovery of yeast and pseudohyphae or hyphae of *Candida* species in superficial crusts or pustules is critical diagnostically. Organisms may be found on routine examination with hematoxylin and eosin (HE), but are more obvious with the use of periodic acid–Schiff (PAS) stain which reveals brilliant magenta, oval-shaped, budding yeast, measuring 3 to 4 μm in diameter, as well as tangled pseudohyphae. Inflammation and yeast colonization may extend to superficial hair follicles (Scott et al., 2001).

Dermal inflammation is superficial perivascular to interstitial, and mixed, and includes a prominent component of neutrophils, with mixtures of lymphocytes, plasma cells and macrophages. Dermal edema is variable but is usually mild to moderate.

The pustular and crusting inflammation of candidiasis is reminiscent of superficial spreading pyoderma but is generally more severe. Discovery of yeast is required for definitive diagnosis. Superficial pustular dermatophytosis may resemble candidiasis. It may be difficult to differentiate pseudohyphae and hyphae of candidiasis from hyphae of dermatophytic origin. The concurrent presence of budding yeast indicates likely candidiasis; however,

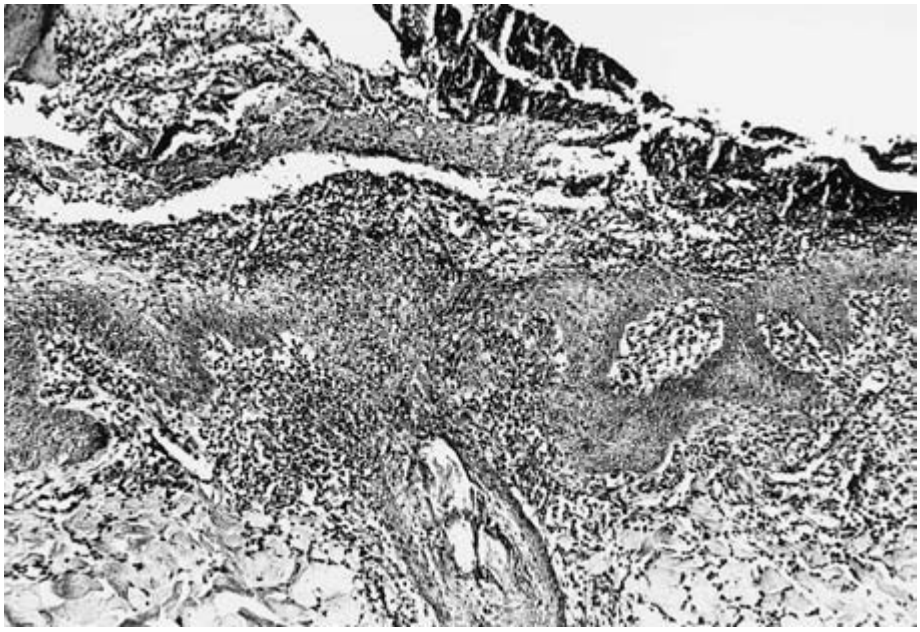

Fig. 1.11 Candidiasis in a dog. A large superficial pustule is accompanied by marked epidermal edema.

Fig. 1.12 *Candida* sp. in superficial keratin (periodic acid–Schiff).

culture is required for definitive differentiation. Candidiasis can complicate superficial necrolytic dermatitis; lesions compatible with superficial necrolytic dermatitis (see Chapter 4) should be searched for in specimens with superficial yeast colonization.

SUPERFICIAL PUSTULAR DERMATOPHYTOSIS

(Synonym: keratin-colonizing dermatophytosis)

Clinical features (Figure 1.13)

Superficial pustular dermatophytosis is an uncommon, predominantly facially-oriented skin disease seen occasionally in the dog. It is caused by keratin-colonizing dermatophytes that affect the surface stratum corneum or superficial follicular keratin preferentially over hair. A similar but even more rare syndrome is seen in cats. The zoophilic dermatophyte *Trichophyton mentagrophytes* is isolated in most reported cases. *Trichophyton mentagrophytes* var. *erinacei* may be the most common keratinophilic dermatophyte seen in the dog (Fairley, 2001). The European hedgehog is the natural host for *Trichophyton mentagrophytes* var. *erinacei*, which has been reported to cause facially-oriented dermatophytosis in dogs in Europe, Great Britain, and New Zealand (Fairley, 2001). However, other dermatophytes (*Trichophyton terrestre*, *Microsporum persicolor*, and *Epidermophyton floccosum*) also have been cultured less frequently.

This syndrome is distinct from most cases of dermatophytosis. Clinically it mimics facially oriented autoimmune skin disease, and histologically it is characterized in part by superficial neutrophilic pustules, sometimes with acantholysis. It has been theorized that in humans and in dogs, acantholysis results from complement-mediated, transepidermal neutrophilic chemotaxis, as well as proteolytic enzymes secreted by the dermatophyte (Poisson et al., 1998). Also, these dermatophytes may be less well adapted to canine and feline hosts, and thus induce a more florid cell-mediated response (Parker & Yager,

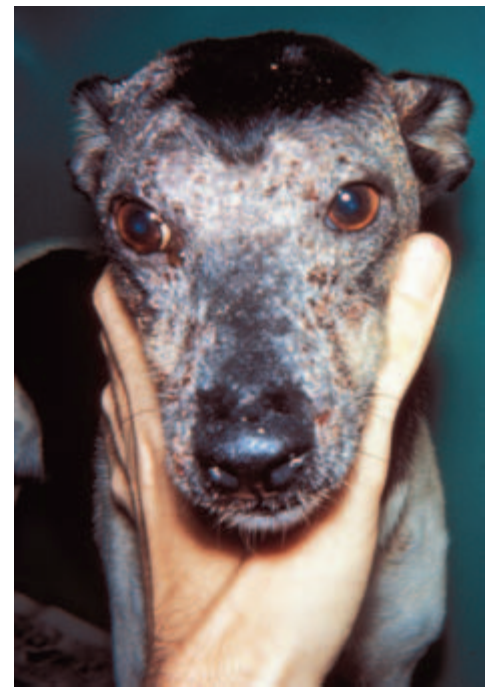

Fig. 1.13 Superficial pustular dermatophytosis in a dog. Lesions are bilaterally symmetric affecting both the haired skin and the planum nasale of the muzzle. (Photograph courtesy A.A. Stannard.)

1997). Superficial pustular dermatophytosis has also been seen occasionally as a more generalized disease in dogs with severe systemic illness that may have been immunosuppressed: these dogs have shown a poor response to therapy. Severe, generalized superficial pustular dermatophytosis has been reported secondary to pituitary dependent hyperadrenocorticism (Chen & Su, 2002).

Clinical features include pustules that rapidly rupture, giving rise to inflamed erythematous papules and plaques with copious adherent crusts. Intact pustules, when present, vary in size from 1 to 5 mm. Larger pustules may be asymmetric and not completely circular. Erosions and ulceration may be present. Lichenification, alopecia, and hyperpigmentation occur rapidly with chronicity. Lesions gradually extend into adjacent normal skin. Rarely, similar lesions have been seen in cats.

The most common site of involvement is the face, including the dorsal and lateral muzzle, and the periorbital region. Unlike other facial dermatophyte infections, the planum nasale may occasionally be affected. Bilateral symmetry is common with facial orientation. Other regions of the body may be affected. Pawpads and the margins of pawpads may be affected in dogs with superficial necrolytic dermatitis (see Chapter 4).

The Fox Terrier and Manchester Terrier may be at increased risk. Three of four affected dogs reported recently from New Zealand were Bull Terriers (Fairley, 2001). Age and sex predilections have not been noted.

Clinical differential diagnoses include facially-oriented autoimmune skin diseases such as pemphigus foliaceus and pemphigus erythematosus, demodicosis, and other dermatophyte infections. In contrast to facially-oriented autoimmune skin disease, superficial pustular dermatophytosis usually does not violate the planum nasale and alter the normal cobblestone appearance. Facial superficial pustular dermatophytosis is much more likely to be bilaterally symmetric than demodicosis. Dermatophyte culture and skin biopsy are recommended for definitive diagnosis.

Biopsy site selection

Intact pustules should be sampled if present. If only chronic crusted lesions remain, care should be taken to include the crusts. The pathology service should be instructed to process any nonadherent crusts.

Histopathology (Figures 1.14 and 1.15)

This form of dermatophytosis is characterized by superficial epidermal pustules. Although most often small, they may be large and broad, resembling those of pemphigus foliaceus. The degree of acantholysis is relatively mild in most cases, but in some canine cases it may be prominent. Superficial pustular dermatophytosis with minimal to no acantholytic cells has been seen in cats. There is variable, sometimes severe, hyperkeratosis of the epidermis and superficial hair follicles; keratin is colonized by dermatophytic spores and hyphae. Organisms may be difficult to identify with hematoxylin and eosin (HE), and are best found using periodic acid–Schiff (PAS) or Gomori's methenamine silver (GMS) stains. These demonstrate typical magenta (PAS) or black (GMS) dermatophytic hyphae and spores within keratin of the epidermis and hair follicles, sometimes in small numbers, but often numerous. In dogs, the dermatophytes very rarely invade hair shafts, leading to the alternate designation of this

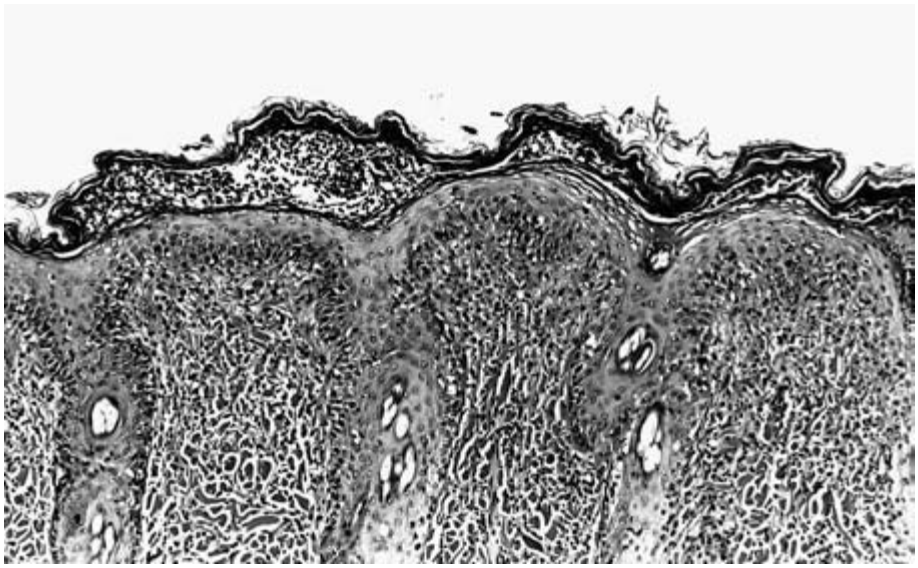

Fig. 1.14 Superficial pustular dermatophytosis in a cat. Note broad subcorneal pustule.

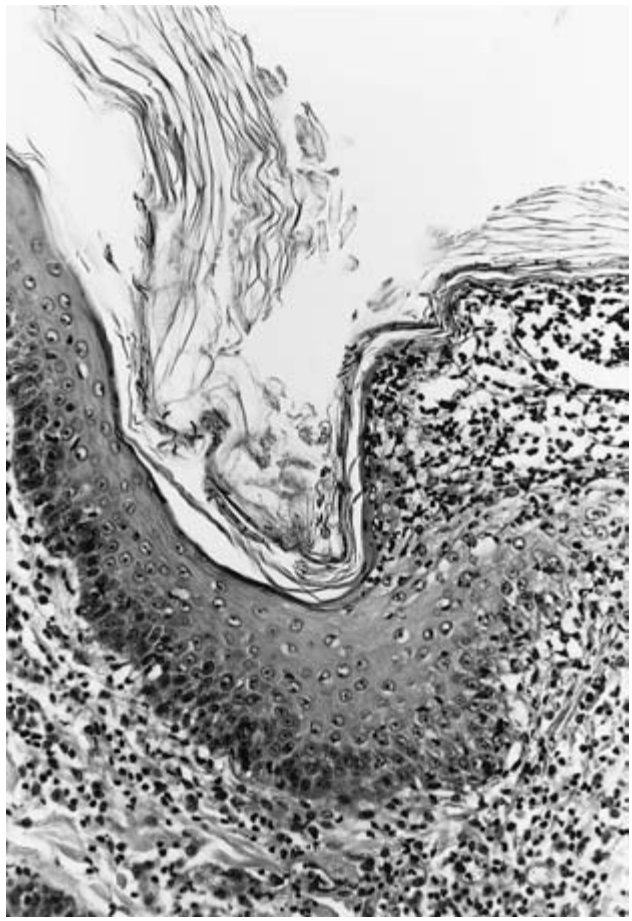

Fig. 1.15 High magnification of superficial pustular dermatophytosis in a cat. Keratin-colonizing dermatophytes are within a follicular ostium adjacent to the edge of a superficial pustule (periodic acid–Schiff).

form of dermatophytosis as 'keratin-colonizing dermatophytosis'. In cats, typical invasion of hair shafts usually is present and organisms are generally easier to see, even on HE evaluation (see Chapter 16).

There may be hyperkeratosis without inflammation in rare biopsy specimens, notably in cats. Dermatophytes may be sparse in these cases; careful search using a PAS or GMS stain, if necessary, should always be made, particularly when obtained from a cat with scaling or alopecia reported as clinical findings.

Superficial dermal inflammation is perivascular to interstitial, and includes neutrophils and mixed mononuclear cells. In some canine cases there may be a band-like pattern of dermal inflammation, including lymphocytes and plasma cells, that may be either lichenoid (without basal cell damage) or interface (with basal cell damage; see Chapters 3 and 11) (Parker & Yager, 1997). Inflammation often extends to the wall of the hair follicles (mural folliculitis; see Chapter 18). In addition, pustular

Fig. 1.16 Pemphigus foliaceus in a cat. Note symmetrical crusting and alopecia. (Photograph courtesy A.C. Mundell; case material University of California, Davis.)

folliculitis or pyogranulomatous furunculosis may be observed.

Differential diagnoses include pemphigus foliaceus, superficial spreading pyoderma, and candidiasis. Pemphigus foliaceus features more acantholysis than most cases of superficial pustular dermatophytosis. Superficial spreading pyoderma demonstrates blue line formation (see p. 6), which is absent in superficial pustular dermatophytosis. Pustular folliculitis, when present, is suggestive of dermatophytosis, particularly in cats. The presence of concomitant mural follicular inflammation also is a feature of this type of dermatophyte infection (see Chapter 18). In all cases demonstration of fungi is required for definitive diagnosis. Culture may be required to differentiate superficial pustular dermatophytosis from candidiasis.

PEMPHIGUS FOLIACEUS

Clinical features (Figures 1.16 through 1.18)

Pemphigus foliaceus (PF) is an uncommon bullous autoimmune skin disease of dogs and cats that affects the epidermis and hair follicles. Desmoglein 1 (Dsg 1) is the primary targeted autoantigen in canine PF, as in humans (Suter et al., 1993; Iwasaki et al., 1997); other antigens in addition to Dsg 1 may be targeted. Autoantibodies bind to Dsg 1, which is a prominent component of the desmosomes in the superficial layers of the epidermis and hair follicles. In humans, the clinical phenotype of the pemphigus group of diseases is defined by the antidesmoglein autoantibody profile; mucosal-dominant pemphigus

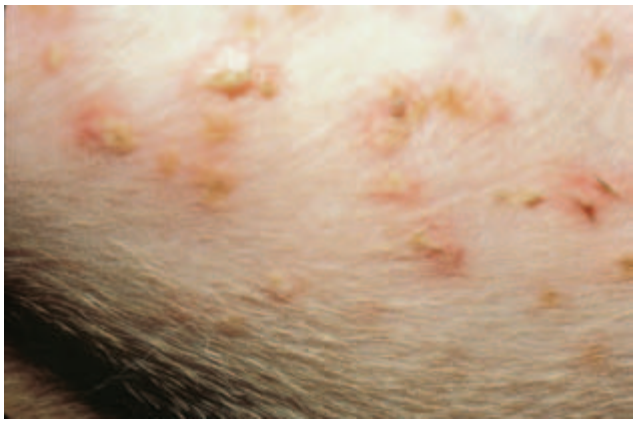

Fig. 1.17 Pemphigus foliaceus in a dog. Multiple intact and recently ruptured vesicopustules are more irregular in contour than most pustules caused by bacterial pyoderma.

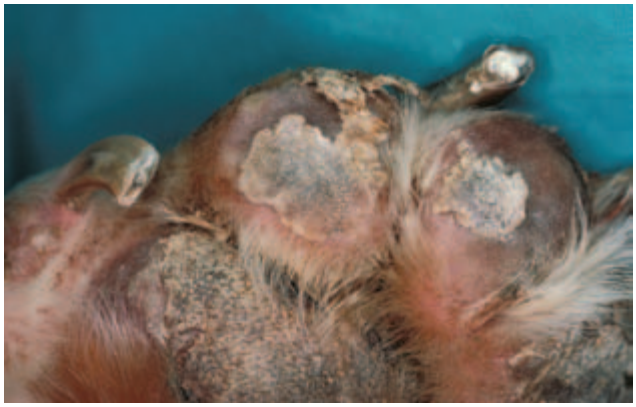

Fig. 1.18 Canine pemphigus foliaceus restricted to the pawpads. Keratinous crusts peel away from intact normal-appearing pad, demonstrating the wave-like progression of the disease.

vulgaris, mucocutaneous pemphigus vulgaris, and PF all have different and distinctive antidesmoglein autoantibody profiles (Amagai et al., 1999). A similar circumstance probably exists in the dog. Pemphigus foliaceus is likely a heterogeneous immunological disease, which may explain the clinical and histological variations observed (Olivry, T.O., personal communication, 2001).

The exact pathomechanism of vesicle and bulla formation is not known. However, loss of intercellular cohesion leads to acantholysis resulting in superficial vesicles and bullae. Plakoglobin may conceivably play a role, as has been demonstrated in the similarly acantholytic disease, pemphigus vulgaris, in dogs (Calhedari et al., 2001). Antikeratinocyte IgG4 autoantibodies may be relevant to the pathogenesis of PF in dogs, as circulating IgG4 antibodies were noted in 80% of dogs with the disease and decreased in 67% of dogs in remission due to immunosuppressive therapy (Hogan et al., 2002). In humans, apoptosis following cellular detachment (termed 'anoikis') characterizes pemphigus, and may be related to increased Fas ligand (FasL) in patients' sera; FasL/Fas interaction on keratinocytes is a major trigger of the extrinsic apoptotic pathway (Puviani et al., 2003). Apoptosis is characteristic of PF in animals as well (see below).

Drug-related, PF-like disease can occur. The term 'pemphigus foliaceus-like drug reaction' may be used when clinical, histopathologic, and immunopathologic features mirror naturally occurring PF, and the disease disappears when the offending drug is discontinued. The term 'drug-induced pemphigus foliaceus' may be used when clinical, histopathologic, and immunopathologic features mirror naturally occurring PF, and the disease continues after drug withdrawal. Drug-related PF (both PF-like drug reaction and drug-induced PF) is reported as a sequela to the administration of various antibiotics (trimethoprim-potentiated sulfonamides, cephalexin) (White et al., 2002). The authors have seen methimazole initiate drug-related PF in cats. To qualify for categorization as drug-related PF, the skin disease must closely mimic the naturally occurring disease, clinically, histopathologically, and immunopathologically. However, possible markers for drug-related PF include unusually rapid onset, very early age of onset, oral lesions, and any other features atypical for naturally occurring disease. Some overlap occurs between drug-related PF and superficial pustular drug reactions (see p. 23). If clinical, histopathological and immunopathological parameters stray too far from those seen with naturally occurring PF, then the term 'superficial pustular drug reaction' may be more appropriate.

Transient superficial pustules (or vesicopustules) develop in waves. Individual pustules may be large (2 to 6 mm in diameter) and vary in color from translucent, to gray-white, to yellow. Coalescence of pustules leads to visually distinct intact pustules or vesicopustules with irregular, asymmetric, polycyclic borders. Pustules frequently span multiple hair follicles, and multiple hairs may protrude from individual pustules. Animals may progress from absence of lesions to sudden development of dozens of pustules. Pustules quickly eventuate in thick, adherent crusts with marked exfoliation. These exfoliative crusts are the most common clinical lesions of PF. Rarely, erosions from ruptured pustules may exhibit targetoid or polycyclic patterns. Alopecia is variable. Generalized erythroderma may be seen. Characteristic pawpad lesions in dogs consist of erythematous swelling at the pad margins, and cracking and villous hypertrophy of the pads. Whitish discoloration beneath the surface of the pad may indicate an intact subcorneal pustule. Pruritus is noted in less than one-half of affected dogs. Photophobia may be noted but is unexplained. In contrast to

canine lesions, feline lesions usually are much milder in severity. In the cat, pustules and vesicles eventuate very rapidly in erosions with adherent yellowish crusts.

The most common sites of involvement in the dog are the dorsal muzzle, planum nasale, pinnae, periorbital skin, and pawpads. Pawpad lesions vary considerably in severity but almost always are present. Truncal lesions are variable but may be diffuse. Striking bilateral symmetry is a common and key feature. Occasionally, the disease may be predominantly confined to the face (see below) or pawpads. Less commonly, mucocutaneous junctions can be affected. One author (P.J.I.) has seen two dogs with lesions of PF confined to the lip folds; another dog had lesions confined to the medial surface of both pinnae. In cats, lesions are less widespread and often are restricted to the muzzle, planum nasale, ear pinnae, around the nipples, and the distal extremities, especially affecting the ungual folds of the claws and pawpad margins. As in dogs, one author (T.L.G.) has seen perioral lesions just at the juncture of the lips. The authors have also seen two cats with histologically typical lesions confined to one extremity.

A clinically distinctive subset of PF, termed 'facially-predominant pemphigus foliaceus', is seen in the Chow Chow, Akita, and occasionally in other breeds. One author (E.J.W.) has observed several cases in Siberian Huskies. Bilaterally symmetric facial lesions are characterized by increased severity with ulceration. Lesions of lesser severity may be seen on the trunk and elsewhere. An additional clinically distinctive subset characterized by widespread truncal pustules with or without facial or pedal involvement may occur more commonly in the Cocker Spaniel and the Chihuahua.

The Bearded Collie, Akita, Chow Chow, Newfoundland, Schipperke, and Doberman Pinscher are genetically predisposed. More recently, the English Springer Spaniel, Chinese Shar Pei, and Collie also have been shown to be at increased risk (Kuhl et al., 1994). Facially-predominant PF is seen more commonly in the Chow Chow and Akita. Canine PF usually is a disease of middle age, but dogs of any age may be affected. The mean age of onset is 4 years with two-thirds of dogs developing lesions at or before 5 years of age (Ihrke et al., 1985). Sex predilections have not been noted. Age, sex, or breed predilections have not been reported for the cat. Some cases of PF may occur as a consequence of chronic, on-going inflammatory skin disease; dogs that developed PF often had a history of long-term inflammatory skin disease (Pascal et al., 1995).

Superficial bacterial folliculitis is the major clinical differential diagnosis for PF. Pustules seen with PF usually are larger and more irregular in contour than the pustules seen with superficial bacterial folliculitis, which tend to be more circular. Pemphigus foliaceus also can appear visually similar to other crusting, pustular and exfoliative skin diseases, such as superficial pustular dermatophytosis, (follicular) dermatophytosis, lupus erythematosus, demodicosis, zinc-responsive dermatosis, sebaceous adenitis, and mycosis fungoides (epitheliotropic malignant T cell lymphoma; see Chapter 37). However, the frequent bilateral symmetry and periodic 'waves' of pustules observed in PF are important differentiating features. When bilaterally symmetric facial lesions are present, the involvement of both haired skin and the non-haired planum nasale is a key differentiating feature of PF. Drug-induced PF may be indistinguishable from classic PF; other superficial pustular drug reactions (not histologically compatible with PF) may partially resemble PF (see p. 23). Superficial pustular dermatophytosis may be the most difficult disease to distinguish from canine PF, and dermatophytosis also may be the most problematic differential diagnosis in the cat. Positive Tzanck preparations from intact vesicopustules or pale central regions on pawpads may document the presence of individual acantholytic cells or rafts of acantholytic cells. Histopathology is required to confirm the diagnosis.

Biopsy site selection

Because of the fragile and transient nature of primary lesions in PF, early lesions (pustules and vesicopustules) should be obtained promptly. Diagnostic histopathology may not be forthcoming from older crusted lesions. If only crusted lesions are available, these should be procured carefully, and the pathology service should be instructed to include any dissociated crusts in the slide preparation. Sites directly adjacent to early pustules should be sampled for direct immunofluorescence or immunohistochemical testing.

Histopathology (Figures 1.19 and 1.20)

Broad, discrete, subcorneal or intragranular pustules within a variably acanthotic epidermis are the typical histopathologic lesions of PF. Pustules often span several follicles and may extend into the follicular infundibula. Mural pustular follicular inflammation may occur (see Chapter 16). Pustules are composed of neutrophils and often eosinophils. Individualized, rounded, often brightly eosinophilic, acantholytic keratinocytes are present in small to large numbers within pustules. Free floating 'rafts' of partially adherent acantholytic cells and adherence of acantholytic cells to the overlying stratum corneum are both characteristic histopathologic features of PF. Neutrophils may encircle and cling to individual acantholytic cells. Active acantholysis, characterized by rounding up of keratinocytes, which appear to be 'springing' from the underlying epidermis, are found beneath pustules. Rarely, acantholysis without pustule formation

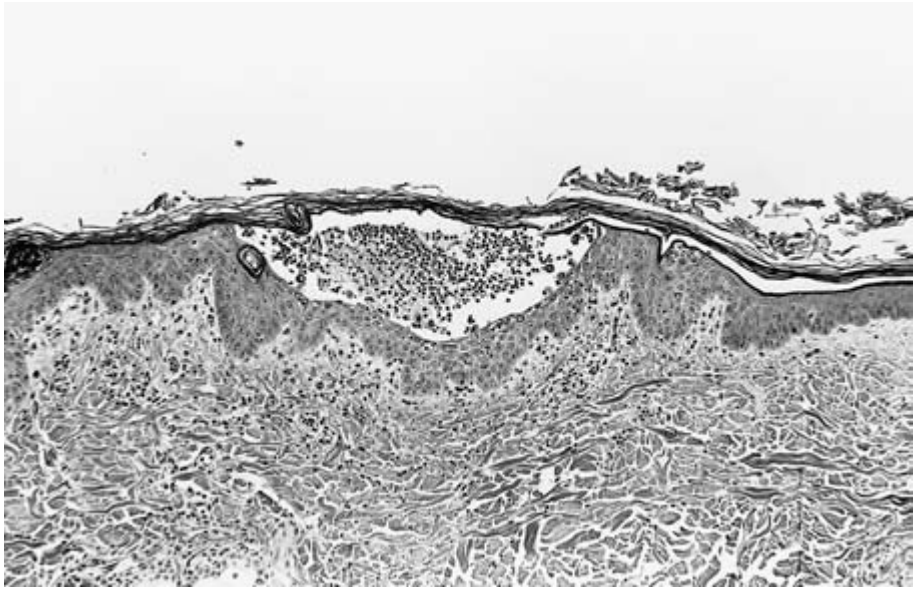

Fig. 1.19 Canine pemphigus foliaceus. A subcorneal pustule contains acantholytic cells.

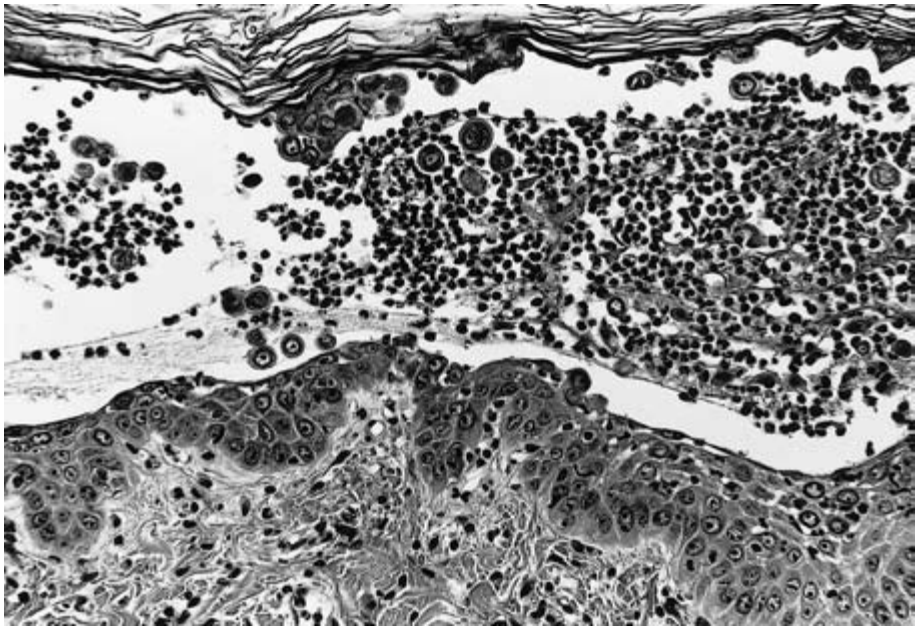

Fig. 1.20 High magnification of subcorneal pustule from a dog with pemphigus foliaceus. Prominent acantholytic cells are free-floating; partially acantholytic cells are adhered to the roof of the pustule.

may be seen in the superficial epidermis; these lesions resemble a 'crumbling brick wall'. In these lesions, affected keratinocytes are hypereosinophilic, slightly rounded, and separated from the underlying epidermis.

Because pustules are transient, active acantholysis and pustulation often are not present in biopsy specimens; the diagnosis may then depend upon the demonstration of degenerated free keratinocytes in crusts. Some caution is warranted in relying on free keratinocytes alone for the diagnosis of PF since spongiosis, as seen in superficial pyoderma and other inflammatory diseases of the epidermis, can also result in separation of keratinocytes from the underlying epidermis, and their ultimate shedding into crusts. Keratinocytes that are disconnected via spongiotic mechanisms may appear less rounded and more ragged or angular than typical acantholytic cells in early stages, but may be indistinguishable once they are within aged crusts. As a further complication, spongiosis rather than acantholysis may be prominent at the base of otherwise typical pustules of PF.

Facially-predominant PF, as seen in Chow Chows, Akitas, and other breeds, is a deeper inflammatory process that frequently involves the wall of hair follicles, often in full thickness distribution ('panfollicular pem-